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Health and Environmental Effects Profile for Dichloroethanes

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR DICHLOROETHANES

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16. ABSTRACT

The Health and Environmental Effects Profile for dichloroethanes was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Dichloroethanes have been evaluated as a carcinogen. The human carcinogen potency factors (q_1^*) for 1,1-dichloroethane and 1,2-dichloroethane are 9.1×10^{-2} $(mg/kg/day)^{-1}$ and 6.9×10^{-2} $(mg/kg/day)^{-1}$, respectively, for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for 1,1- and 1,2-dichloroethane is 1000.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AFC	Antibody forming cells
BCF	Bioconcentration factor
BOD	Biochemical oxygen demand
BSP	Bromosulphalein
bw	Body weight
CAS	Chemical Abstract Service
CHO	Chinese Hamster ovary
CNS	Central nervous system
CS	Composite score
DNA	Deoxyribonucleic acid
EC_{50}	Concentration effective to 50% of recipients (and all other subscripted dose levels)
K_{oc}	Soil sorption coefficient
K_{ow}	Log octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
MATC	Maximum acceptable toxicant concentration
MED	Minimum effective dose
NADH	Nicotinamide adenine dinucleotide (reduced form)
NADPH	Nicotinamide adenine dinucleotide phosphate
NOEC	No-observed-effect concentration
NOEL	No-observed-effect level
PMA	Phorbol myristate acetate

LIST OF ABBREVIATIONS (cont.)

ppb	Parts per billion
ppm	Parts per million
ppt	Parts per thousand
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvate transaminase
STEL	Short-term exposure level
TLV	Threshold limit value
TWA	Time-weighted average
UDS	Unscheduled DNA synthesis

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

1,1-Dichloroethane and 1,2-dichloroethane are substitution products of ethane in which two of the hydrogen atoms have been replaced by two chlorine atoms. 1,1-Dichloroethane is also known as ethylidene chloride and ethylidene dichloride (Verschueren, 1983). Some of the common synonyms for 1,2-dichloroethane are ethylene dichloride, EDC, dichloroethylene, DCE, ethylenechloride and S-dichloroethane (Verschueren, 1983; Archer, 1979). The structures of the two compounds are given below.

	$H_3C\text{-}CHCl_2$	$ClH_2C - CH_2Cl$
	1,1-dichloroethane	1,2-dichloroethane
Empirical formula:	$C_2H_4Cl_2$	$C_2H_4Cl_2$
Molecular weight:	98.96	98.96

The CAS Registry numbers for 1,1-dichloroethane and 1,2-dichloroethane are 75-34-3 and 107-06-2, respectively.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

1,1-Dichloroethane is a colorless liquid with an ethereal odor (Archer, 1979). 1,2-Dichloroethane is also a colorless, oily liquid with a chloroform-like odor (Hawley, 1981). Both compounds are soluble in common organic solvents, including other chlorinated solvents (Archer, 1979). Some of the physical properties of both compounds are listed in Table 1-1.

1,1-Dichloroethane undergoes dehydrochlorination reaction in the presence of catalysts when oxidized at reflux temperature; 1,1-dichloroethane produces hydrogen chloride. It reacts with amine to yield small amounts of the dimer butane (Archer, 1979). The hydrolysis of 1,2-dichloroethane at

TABLE 1-1

Relevant Physical Properties of 1,1-Dichloroethane and 1,2-Dichloroethane[a]

Parameter	1,1-Dichloroethane	1,2-Dichloroethane
Melting point, °C:	-96.7	-35.3
Boiling point, °C:	57.3	83.7
Density at 20°, g/mℓ:	1.175	1.253
Explosive limits in air at 25°C:	5.4-11.4% by volume	6.2-15.6% by volume
Vapor pressure at 20°C:	182 mm Hg	64 mm Hg
Solubility in water at 20°C:	5500 mg/ℓ	8690 mg/ℓ
Log K_{ow}:[b]	1.79	1.48
Henry's Law constant (atm m^3mol^{-1}):[c]	4.26×10^{-3}	9.14×10^{-4}
K_{oc} standardized with respect to soil organic content:[d]	58	19-83
Conversion factor at 20°C:	1 ppm	4.11 mg/m^3

[a] Source: Archer, 1979; Verschueren, 1983

[b] Yoshida et al., 1983

[c] Mabey et al., 1981

[d] Kenaga, 1980; Chiou et al., 1979; Sabljic, 1984; Koch, 1983

elevated temperatures (≥60°C) produces ethylene glycol. Atmospheric oxidation of 1,2-dichloroethane at room temperature or at a higher temperature generates hydrogen chloride; it also undergoes nucleophilic substitution reactions (Archer, 1979).

1.3. PRODUCTION DATA

Commercially, 1,1-dichloroethane is produced from hydrogen chloride and vinyl chloride at 20-55°C in the presence of a catalyst. The production of vinyl chloride and of 1,1,1-trichloroethane through photochlorination also produces 1,1-dichloroethane as an intermediate (Archer, 1979). The two commercial processes that account for almost all of the 1,2-dichloroethane produced currently are the direct catalytic vapor or liquid-phase chlorination of ethylene at 40-50°C with 5% added air, and the oxychlorination process in which ethylene, hydrogen chloride and oxygen are reacted in the presence of a catalyst to form 1,2-dichloroethane (Archer, 1979).

According to a NIOSH (1978a), 1,1-dichloroethane is probably not produced commercially in the United States. The United States producers of 1,2-dichloroethane and their production capacity as of January, 1984 are listed in Table 1-2. The 1982 and 1983 United States production of 1,2-dichloroethane was 9.73 and 11.51 billion pounds, respectively (USITC, 1984). It was the 17th highest volume chemical produced in the United States in 1979 (Anonymous, 1980). The major portion of 1,2-dichloroethane produced in the United States is consumed captively by the producers, and in 1983 <10% of the total production was sold on the open market (USITC, 1984).

TABLE 1-2

United States Production of 1,1-Dichloroethane and 1,2-Dichloroethane*

Manufacturer and Location	Annual Capacity (million pounds)
Atlantic Richfield Co. Port Arthur, TX	500
Boden, Inc. Geismar, LA	510
Diamond Shamrock Corp. Deer Park, TX	190
Dow, USA	
Freeport, TX	1,600
Oyster Creek, TX	1,215
Plaquemine, LA	2,065
DuPont (CONOCO) Lake Charles, LA	1,155
Ethyl Corp.	
Baton Rouge, LA	225
Pasadena, TX	700
Formosa Plastic Corp.	
Baton Rouge, LA	550
Point Comfort, TX	850
Georgia-Pacific Corp. Plaquemine, LA	1,650
Goodrich Co.	
LaPorte, TX	1,585
Calvert City, KY	1,000
Convent, LA	800
PPG Industries Lake Charles, LA	2,700
Shell Chemical Co. Deer Park, TX	1,400

TABLE 1-2 (cont.)

Manufacturer and Location	Annual Capacity (million pounds)
Union Carbide Corp.	
Taft, LA	150
Texas City, TX	150
Vulcan Materials Co.	
Geismar, LA	350
Total	19,345

*Source: SRI, 1984

1.4. USE DATA

The largest industrial use of 1,1-dichloroethane is in the production of 1,1,1-trichloroethane (Archer, 1979). It is also used as a solvent; in paint, varnish and finish removers; in metal degreasing; in organic synthesis; and in ore flotation (Verschueren, 1983). A major portion (~83%) of 1,2-dichloroethane in the United States is used in the production of vinyl chloride. It is also used in the production of 1,1,1-trichloroethane, trichloroethylene, vinylidene chloride, and perchloroethylene and ethylenediamines. As a lead scavenger, it is used as an additive in leaded fuels. Other miscellaneous applications of 1,2-dichloroethane include use in solvents for various extraction and cleaning purposes in organic synthesis, as a dispersant in rubber and plastics, as wetting and penetrating agents, in ore flotation and as a grain fumigant (Archer, 1979; NIOSH, 1978a).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. ATMOSPHERE

Reaction with OH· radicals is the principal mechanism by which many organic compounds are removed from the atmosphere. The estimated rate constants for 1,1- and 1,2-dichloroethane reactions with OH· radicals at 27°C are 0.26×10^{-12} and 0.22×10^{-12} cm^3 $molecule^{-1}$ sec^{-1}, respectively (Singh et al., 1981). Assuming these rate constants and a tropospheric OH· radical concentration of 10^6 molecules cm^{-3} (Singh et al., 1981), the half-lives of 1,1- and 1,2-dichloroethane in the troposphere are 31 and 36 days, respectively.

In a smog chamber study to determine the relative reactivity of volatile organic compounds toward photochemical smog formation, Sickles et al. (1980) estimated that the reactivity of 1,2-dichloroethane toward NO_x is slower by a factor of 0.57 compared to propane reaction with NO_x at a hydrocarbon to NO_x ratio of 20. At this hydrocarbon to NO_x ratio, Dimitriades and Joshi (1977) reported that an average of 2% of propane disappeared in 1 hour as a result of its reaction with NO_x. Assuming a first-order disappearance of propane, the estimated half-life of propane from its reaction with NO_x is ~3 days. If the NO_x reaction with 1,2-dichloroethane is assumed to be 0.57 times slower, the half-life for this reaction may be ~5 days; however, the ratio of hydrocarbon to NO_x in ambient air is ~8-10, and at this ratio propane does not react with NO_x (Farley, 1977). Consequently, under normal atmospheric conditions, the reaction of 1,2-dichloroethane with NO_x may not be significant.

The reactivity of 1,2-dichloroethane with chlorine atoms was studied by Bertrand et al. (1971), who determined that the chlorine-sensitized photooxidation of gas phase 1,2-dichloroethane was not significant. Although the relative reactivity of 1,1-dichloroethane toward chlorine-sensitized photooxidation is ~4 times faster than 1,2-dichloroethane (Spence and Hanst, 1978), no quantitative estimate regarding the significance of this reaction in the atmosphere can be given because of the lack of kinetic data. Hydrochloric acid, CO, CO_2 and formyl chloride were formed as a result of chlorine photooxidation of both 1,1- and 1,2-dichloroethane (Spence and Hanst, 1978). In addition, phosgene and acetyl chloride in the case of 1,1-dichloroethane, and chloroacetyl chloride in the case of 1,2-dichloroethane were also formed (Spence and Hanst, 1978).

The direct photolysis of either compound in the atmosphere is unlikely because they do not absorb light at wavelengths >290 nm (Callahan et al., 1979).

Cupitt (1980) considered the possibility of the removal of 1,2-dichloroethane from the atmosphere by dissolution into rain droplets, dry deposition and adsorption on aerosols, and concluded that the physical removal probability is unlikely. Judging from its higher volatility and lower aqueous solubility (see Section 1.2.), the probability of significant 1,1-dichloroethane removal from the atmosphere through physical processes is even less likely.

2.2. WATER

The fates of 1,1- and 1,2-dichloroethane with respect to their possible photochemical and hydrolysis reactions were reported by Callahan et al. (1979). Neither of these reactions is expected to be significant in determining the fate of 1,1- and 1,2-dichloroethane in aquatic media (Callahan et al., 1979; Mabey et al., 1981). Based on the rate constant data reported by Mabey et al. (1981) and the concentration of free radicals in aquatic media reported by Mill et al. (1980), the oxidation of 1,1- and 1,2-dichloroethane by singlet oxygen ($K << 360\ M^{-1}\ hr^{-1}$ and $<360\ M^{-1}\ hr^{-1}$, respectively) and peroxy radicals ($K=1$ and <1, respectively) can be predicted to be environmentally insignificant processes.

The biodegradation of 1,1-dichloroethane in natural aquatic media has not been studied comprehensively. From a static-culture flask-screening procedure with settled domestic wastewater as microbial inoculum, Tabak et al. (1981) reported significant degradation of 1,1-dichloroethane with rapid adaptation. The unadapted microorganisms decomposed 50% of the compound in 7 days, while acclimated microorganisms decomposed 78% of the compound in 7 days. Although Tabak et al. (1981) suggest that 1,1-dichloroethane may biodegrade significantly under biological treatment of wastewater, it is difficult to predict the biodegradation fate of this compound in ambient aquatic media.

The biodegradability of 1,2-dichloroethane in aquatic media has been studied by several authors. Based on 5-day BOD tests, Price et al. (1974) reported 18% degradation of 1,2-dichloroethane in freshwater in 10 days with non-acclimated microorganisms. The degradation was reported to be 7% in 10 days with salt water. Kincannon et al. (1983), however, observed no biodegradation of 1,2-dichloroethane by activated sludge with a mean cell residence time of ~3 days. Tabak et al. (1981) reported slow to moderate biodegradation activity for 1,2-dichloroethane with settled domestic wastewater as microbial inoculum. At a concentration of 5 mg/ℓ, only 26% of the compound biodegraded in 7 days with unacclimated microorganisms. The degradation rate was higher (41%) with acclimated microorganisms. From both modified shake flask and river die-away tests, Mudder (1982) reported no significant degradation of 1,2-dichloroethane in 21 days at an original substrate concentration ≥ 1 ppm. If the biodegradation rate constant of

1×10^{-10} mℓ $cell^{-1}$ hr^{-1} (Mabey et al., 1981) and the concentration of microorganisms in water of 10^5 cell $mℓ^{-1}$ (Banerjee et al., 1984) are assumed, the biodegradation of 1,2-dichloroethane in ambient aquatic media will probably be an insignificant process.

Dunn and Hutton (1983) reported that 99% of the 1,2-dichloroethane in industrial wastewater at an initial concentration of <1 ppm was removed by the combined powdered activated carbon-activated sludge (PACT) process. The average concentration of 1,2-dichloroethane in the treated effluent was 6.2 ppb. It is difficult to describe the contribution of biodegradation in the removal process since volatilization and sorption played significant roles in the removal of 1,2-dichloroethane.

The removal of 1,1- and 1,2-dichloroethane from aquatic media by physical processes, such as volatilization and adsorption onto particulate matter, has been studied by a few investigators. Assuming the Henry's Law constant values given in Section 1.2. and the relationship between volatility and Henry's Law constant given by Lyman et al. (1982), it can be predicted that both compounds will volatilize from the aquatic phase in significant quantities. From their laboratory experiments with a 2 ppm solution, Chiou et al. (1980) estimated the evaporation half-life of 1,2-dichloroethane from a water depth of 1.6 cm to be approximately minutes under a stirring rate of 100 rpm. Under more realistic environmental conditions of wind speed of 3 M/sec and current velocity of 1 M/sec, Lyman et al. (1982) estimated the evaporation half-life of 1,2-dichloroethane at a water depth of 1 M to be 4 hours.

The volatilization half-lives measured in the laboratory are primarily dependent upon the depth of water in the mixing tank and the stirring conditions (Rathbun and Tai, 1984). Therefore, these values cannot be directly applied to natural streams. The usual procedure in transferring the laboratory data to stream conditions is to measure the ratio of the rate of volatilization of the chemical and oxygen reaeration rate under the laboratory conditions. This ratio, usually called the reaeration rate ratio, is then combined with oxygen reaeration rates in natural bodies of water to derive the volatilization half-lives in a natural aquatic system. The reaeration rate ratios for 1,1- and 1,2-dichloroethane have been estimated to be 0.55 and 0.58, respectively (Cadena et al., 1984). Combining these values with the oxygen reaeration rates of 0.19 day^{-1} and 0.96 day^{-1} in pond and river waters, respectively (Mabey et al., 1981), the estimated evaporative half-lives of these chemicals are >1 day and >6 days for river and pond water, respectively. Thus, evaporation from aquatic media may be the most significant removal mechanism for both 1,1- and 1,2-dichloroethane from bodies of water. That removal through volatilization is a significant removal mechanism for the two dichloroethanes from aquatic media was confirmed by the biodegradation studies of Kincannon et al. (1983) and Tabak et al. (1981). Because of their significant volatility, aeration in combination with adsorption has been suggested as a viable method for treatment of drinking water containing 1,1- and 1,2-dichloroethane (Love and Eilers, 1982).

No comprehensive study regarding the adsorption of 1,1- and 1,2-dichloroethane onto sediments was located; however, the K_{oc} values given in Section 1.2. and the study of Richter (1983) show that both 1,1- and 1,2-dichloroethane do not adsorb strongly onto soils. Therefore, it is speculated that sorption of these compounds onto sediments will not be a significant process. The same conclusion regarding the sediment sorbability of these compounds was reached by Callahan et al. (1979). In their biodegradation study, Kincannon et al. (1983) reported only 1% removal of 1,2-dichloroethane through sorption onto sediments, which also proves the poor sorbability of dichloroethane onto sediments.

In a continuous-flow 14-day experiment duration with bluegill sunfish, Lepomis macrochirus, Barrows et al. (1978) determined a BCF of 2.0 for 1,2-dichloroethane. Gossett et al. (1983) collected and analyzed for 1,1- and 1,2-dichloroethane the tissues of several aquatic species, such as halibut, Paralichthys californicus, sanddab, Citharichthys xanthostigma, and Dover sole, Microstomus pacificus, near the discharge zone of the Los Angeles County wastewater treatment plant. Although the combined concentration of 1,1- and 1,2-dichloroethane in the discharged effluent was 44 ppb, the authors failed to detect (detection limit of 0.3-0.5 ppb) any dichloroethane in the tissues of the aquatic organisms. Due to lack of aquatic concentration data of the individual compounds, this study cannot be employed for the evaluation of BCF in tissues of aquatic species; however, it provides evidence that the BCF values of 1,1- and 1,2-dichloroethane in aquatic species may be low.

The BCFs for both 1,1- and 1,2-isomers can be estimated by using the K_{ow} values given in Section 1.2. and the regression equation of Veith et al. (1979): $\text{Log BCF} = 0.85 \log K_{ow} - 0.70$. The estimated values for both compounds obtained is <1. Therefore, the theoretical predictions confirm the experiment observation that neither compound will bioaccumulate in aquatic species.

It can be concluded from the above discussion that the primary mechanism for the removal of 1,1- and 1,2-dichloroethane from aquatic media is volatilization. The volatilization half-life is such that both compounds will persist in aquatic media for a reasonable period and may participate in aquatic transport from one region to another.

2.3. SOIL

Pertinent data regarding the chemical fates of 1,1- and 1,2-dichloroethane in soil were not located in the available literature cited in the Appendix. Based on their reactivities in aquatic media, it is likely that neither compound will undergo significant hydrolysis or photolysis in soil. The biodegradability of 1,2-dichloroethane in a sandy soil under aerobic conditions was found to be negligible (Wilson et al., 1981). No biodegradation study for 1,1-dichloroethane in aerobic soil media was located in the available literature as cited in the Appendix. Based on the biodegradability of this compound in surface water and the biodegradability of 1,2-dichloroethane in soil, it is likely that 1,1-dichloroethane will not biodegrade significantly under aerobic soil conditions. The biodegradability of 1,1- and 1,2-dichloroethane under anaerobic soil conditions was investigated by Bouwer and McCarty (1983) and Wilson et al. (1983a,b). Wilson et al. (1983a,b) reported very little biodegradation of either compound under anaerobic incubation of the compounds for 7 days. Bouwer and McCarty (1983) reported a 63% reduction of 1,2-dichloroethane concentration after 25 weeks of incubation. Haider (1980) reported reductive dichlorination of chlorinated ethanes when incubated anaerobically. The reductive dechlorination of chlorinated methanes and ethanes in soil under anaerobic conditions may be due to the chemical reaction of Fe^{+2} porphyrin present in soil from decaying organisms with the chlorinated hydrocarbons (Klecka and Gonsior, 1984). In the case of 1,1-dichloroethane, however, this chemical reaction was insignificant.

The K_{oc} of 1,2-dichloroethane in soils ranges from 19-83 (see Section 1.2.). Therefore, this compound is not expected to be sorbed strongly to soils. This has been confirmed by Wilson et al. (1981), who reported ~50% percolation of the compound through a 140 cm sandy soil column at a 1,2-dichloroethane concentration of <1 ppm. Similarly, Richter (1983) reported low adsorption of 1,1-dichloroethane in soils. Given the low chemical and microbiological reactivities of these compounds in soils and their low sorption capabilities, both 1,1- and 1,2-dichloroethane are expected to leach through soil. In fact, such leachings of both of these compound from soil have been observed (Sawhney and Kozloski, 1984; Connor, 1984). Leaching data from five Wisconsin and one New York municipal landfill sites show 1,1-dichloroethane to be one of the ubiquitous compounds in the landfill leachates (Connor, 1984)

Few investigative data are available on the volatilization of dichloroethanes from soil surfaces, although volatilization may be the most significant removal mechanism for these chemicals from soil. Based on the volatility from water and on the investigation by Wilson et al. (1981) who reported a 50% loss of 1,2-dichloroethane from a 140 cm soil column through volatilization, it is likely that volatilization is the most significant removal process for both dichloroethanes from soil.

3. ENVIRONMENTAL LEVEL AND EXPOSURE

3.1. AIR

Available data through 1980 regarding the atmospheric levels of 1,2-dichloroethane in urban, rural and industrial sites in the United States were provided by Brodzinsky and Singh (1982). The overall median concentration for 1,2-dichloroethane from all 1675 sampling points was 200 ppt. The median concentrations for 9 rural, 1230 urban and 436 industrial sampling points were 0, 120 and 1200 ppt, respectively (Brodzinsky and Singh, 1982). Bozzelli and Kebbekus (1982) reported a mean atmospheric concentration for 1,2-dichloroethane in samples collected in 1978 from Rutherford, Newark, Piscataway-Middlesex, Bridgewater-Somerset and Somerville-Boundbrook areas of New Jersey to be 470, 660, 120, 180 and 480 ppt, respectively. Samples collected in 1979 from Newark and Camden, NJ, showed trace levels of 1,2-dichloroethane, while the samples from Rutherford and Elizabeth, NJ, showed concentrations of 10 and 40 ppt, respectively (Harkov, 1983). Air samples collected in 1981 from Newark, Elizabeth and Camden, NJ, however, showed no trace of 1,2-dichloroethane (Harkov et al., 1983). Thus, there has been a decreasing trend of 1,2-dichloroethane concentrations in New Jersey atmosphere in recent years.

Singh et al. (1982) monitored the atmospheric concentrations of 1,2-dichloroethane in Staten Island, NY, Pittsburgh, PA, and Chicago, IL, in 1982. The reported mean concentrations were 256, 121 and 195 ppt, respectively. The level of 1,2-dichloroethane in a number of locations in the United States was monitored during 1976-1980 by Shairer et al. (1983). Trace amounts of 1,2-dichloroethane were detected in samples from Charleston, WV, Birmingham, AL, Houston, TX, Baton Rouge, LA, El Paso, TX, and Magna, UT; however, the samples from Elizabeth, NJ, El Dorado, AR, and Upland, CA, contained ~2700 ppt, trace to 2100 ppt and trace to 200 ppt, respectively, of 1,2-dichloroethane. The quantification for 1,2-dichloroethane in this investigation was done by stamen hair mutation response in Tradescantia clone 4430, and the detection limit for the method was not specified. The method is probably less sensitive than the analytical methods presently available.

Levels of 1,2-dichloroethane in three areas that contain production and user facilities for 1,2-dichloroethane were measured during the period 1978-1979 (Elfers et al., 1979). The Lake Charles, LA, sites showed as high as 184 ppb concentration for 1,2-dichloroethane in the ambient air. The average concentration of 1,2-dichloroethane in Lake Charles, LA, was 27.5 ppb. In Calvert City, KY, and New Orleans, LA, ambient concentrations for 1,2-dichloroethane ranged from <0.12-17.8 and <0.12-41.7 ppb, respectively (Elfers et al., 1979).

It is obvious from the above discussion that the ambient levels of 1,2-dichloroethane in rural areas will probably be negligible. Levels of atmospheric 1,2-dichloroethane will be intermediate in urban areas, with a median value of 120 ppt (Brodzinsky and Singh, 1982). The maximum level of atmospheric 1,2-dichloroethane is expected to be found around production and user sites. Brodzinsky and Singh (1982) estimated a median concentration of 1200 ppt around such sites.

Waste disposal sites may also show high levels of atmospheric 1,2-dichloroethane. For example, the Kin-Buc, Edison, NJ, waste disposal site was monitored in 1976 by Pellizzari (1982), who reported a concentration range of trace to 6800 ppt for 1,2-dichloroethane in the ambient air surrounding this site.

Since 1,2-dichloroethane is used as an additive in leaded fuel, another site that is expected to show high levels of this compound is urban areas with high vehicular traffic. The level of 1,2-dichloroethane near a busy street in London, England was reported to be in the range of 117-521 ppt (Tsani-Bazaca et al., 1981). The concentration of 1,2-dichloroethane in auto exhaust emissions from 0.2 g/ℓ of 1,2-dichloroethane added to leaded gasoline was also monitored by these investigators. The emission data from a 3 ℓ Ford Granada and 0.85 ℓ British Leyland Mini showed that both engine type and driving conditions were important in the emission of 1,2-dichloroethane in the exhaust. The automobile with the smaller engine had lower 1,2-dichloroethane emissions than the vehicle with the larger engine. The emission of 1,2-dichloroethane was maximum during a cold start and at idle speed, and minimal at a speed of 50 mph. The corresponding 1,2-dichloroethane emissions for the Ford Granada were reported to be 791, 706 and 82 ppb, respectively.

The concentration of 1,2-dichloroethane measured around a motorway in England, however, showed lower (mean of 20 ppt) levels of the compound than an urban area (mean of 260 ppt) (Clark et al., 1984). This low emission rate at the motorway site was explained as due to the rapid dispersion of the compound because of the high wind speed (Clark et al., 1984). Tsani-Bazaca et al. (1982) also reported low concentrations of 1,2-dichloroethane (ranging from not detected to 50 ppt) in the vicinity of Gatwick airport in England. With the phasing out of leaded fuels for vehicular use, the quantity of 1,2-dichloroethane in the atmosphere arising from vehicular traffic is expected to decrease substantially.

Assuming that the median level of 1,2-dichloroethane in ambient urban air is 120 ppt (~0.5 μg/m^3) and an average individual inhales 20 m^3 of air/day, the average inhalation exposure of 1,2-dichloroethane for an individual living in an urban area will be ~10 μg/day.

The atmospheric levels of 1,1-dichloroethane in urban, rural and industrial sites in the United States through 1980 are available from Brodzinsky and Singh (1982). The median concentration of 1,1-dichloroethane from all sites was 55 ppt, while the median concentrations in 2 rural, 466 urban and 101 industrial sites were 0, 61 and 11 ppt, respectively (Brodzinsky and Singh, 1982).

The ambient atmospheric level of 1,1-dichloroethane around the Kin-Buc, Edison, NJ, waste dosposal site was as high as 5600 ppt (Pellizzari, 1982).

Assuming a median average level of 1,1-dichloroethane in ambient air of 55 ppt (~0.2 μg/m^3) and an average individual inhalation of 20 m^3 of air/day, the inhalation exposure to 1,1-dichloroethane for an individual in the United States will be ~4 μg/day.

3.2. WATER

Both 1,1- and 1,2-dichloroethane have been monitored extensively in water. Sauer (1981) failed to detect 1,2-dichloroethane in water from the open ocean; however, in unpolluted coastal water from the Gulf of Mexico, Sauer (1981) reported a concentration of 50 ng/kg for 1,2-dichloroethane. In polluted coastal water the concentration was reported to be much higher, ranging from 180-120 ng/kg (Sauer, 1981). Rawlings and Samfield (1979) reported a concentration range of 0.6-4 μg/ℓ for 1,2-dichloroethane in secondary effluents from textile plants. Cole et al. (1984) reported a concentration range of 1.5-3 μg/ℓ for 1,1-dichloroethane in storm runoff water from Long Island, NY, and Eugene, OR. Also, 1,2-dichloroethane was detected by these authors in runoff water from Eugene, OR, at a concentration of 4 μg/ℓ. Both 1,1- and 1,2-dichloroethane were reported in the primary, secondary and final effluent from municipal wastewater treatment plants (Young et al., 1983). DeWalle and Chian (1978) collected water from the Delaware basin where the Delaware, Schuylkill and Lehigh Rivers drain, and detected 1,2-dichloroethane at a concentration >1 ppb with a frequency of 33%. The level of 1,2-dichloroethane in water samples that had detectable amounts of this compound were not reported. The levels of both 1,1- and 1,2-dichloroethane in biotreatment effluents and final effluent from wastewater treatment facilities of the petroleum refining industry were reported by Snider and Manning (1982). 1,1-Dichloroethane and 1,2-dichloroethane were not detected at a detection limit of 10 ppb and 1-10 ppb, respectively.

Letkiewicz et al., (1982) discussed the results of six surveys in which a number of chemical pollutants including 1,2-dichloroethane were analyzed in drinking water. The six Federal drinking water surveys were the National Organic Reconnaissance Survey (NORS), the National Organics Monitoring Survey (NOMS), the National Screening Program for Organics in Drinking Water (NSP), the Community Water Supply Survey (CWSS), the Groundwater Supply Survey (GWSS) and the Rural Water Surveys (RWS). Except for the GWSS survey, all other surveys sampled both groundwater and surface waters. The results of these surveys are shown in Table 3-1.

The EPA's GWSS also monitored the levels of 1,1-dichloroethane in 945 water supplies across the United States (Westrick et al., 1984). Of the 945 water supplies, water from 41 supplies showed detectable levels of 1,1-dichloroethane, with a maximum concentration of up to 4.2 μg/ℓ detected in water from one water supply (Westrick et al., 1984). The median concentration for all the samples, however, was less than the detection limit (0.2 μg/ℓ).

TABLE 3-1

Levels of 1,2-Dichloroethane in United States Drinking Waters as Obtained From Six Federal Surveys*

	Groundwater				Surface Water			
			Concentration (μg/ℓ)				Concentration (μg/ℓ)	
Survey	Number Sampled	Number Positive	Range	Mean	Number Sampled	Number Positive	Range	Mean
NORS	16	0	NA	NA	64	6	0.2-6.0	NR
NOMS I	18	0	NA	NA	87	1	2	NA
NOMS II	18	1	0.02	NA	87	1	1.8	NA
NOMS III	NS	NS	NA	NA	87	1	1.25	NA
NSP	13	1	0.2	NA	107	1	3.8	NA
CWSS	312	3	0.57-1.1	NR	110	1	0.62	NA
GWSS	945	14	0.29-9.8	1.6	NA	NA	NA	NA
RWS	633	5	0.5-18	5.6	47	1	19	NA

*Source: Letkiewicz et al., 1982

NA = Not applicable; NR = not reported; NS = not surveyed

In addition to the Federal data, monitoring data from six states are also available on the levels of 1,1- and 1,2-dichloroethane in groundwater. Of the 486 water supplies analyzed for 1,2-dichloroethane, only 46 supplies showed detectable levels of 1,2-dichloroethane (Letkiewicz et al., 1982). A maximum concentration of 2100 μg/ℓ was reported for one sample collected from Elkhart, IN (Letkiewicz et al., 1982). The average concentration of 1,2-dichloroethane in all the samples was ~12.0 μg/ℓ, while the median concentration was below the detection limit (0.5 μg/ℓ). Kopfler et al. (1975) also reported the detection of 1,2-dichloroethane in Cincinnati drinking water.

Data regarding 1,1-dichloroethane in groundwater supplies are also available from Coniglio et al. (1980). Nine states monitored 785 wells for levels of 1,1-dichloroethane. The highest number of samples with detectable levels of 1,1-dichloroethane originated from Florida. Of the 329 wells tested in Florida, 26% showed detectable levels of 1,1-dichloroethane, although neither the concentration range nor the median concentration level was stated.

Other values for the levels of 1,1- and 1,2-dichloroethane in both groundwater and surface water are available. For example, Page (1981) monitored 1066 groundwaters and 104 surface waters in New Jersey during 1977-1979 and detected 1,2-dichloroethane in 606 and 71 samples, respectively. Although the highest concentration in groundwater and surface water was 37 and 305 ppb, respectively, the median concentration was below the detection limit in either case. Connor (1984) reported a concentration range of 1.2-2.1 ppb for 1,2-dichloroethane in contaminated groundwater in Nassau County, Long Island. Fielding et al. (1981) reported the detection of both 1,1- and 1,2-dichloroethane in raw and treated waters in England.

The levels of both 1,1- and 1,2-dichloroethane in leachates from municipal solid waste, contaminated groundwater and presumably uncontaminated groundwater from several Minnesota sites were reported by Sable and Clark (1984). 1,1-Dichloroethane was detected at a concentration range of 0.6-4.6 ppb in 5/6 leachate sites and at a concentration range of 0.5-1900 ppb in 7/13 contaminated groundwaters, but it was undetectable (0.5-0.6 ppb detection limit) in groundwater from seven uncontaminated sites. 1,1-Dichloroethane was also detected by other investigators in 3/5 Wisconsin leachates at a concentration range of 510-6300 ppb and in 1/2 other Minnesota leachates at a concentration of 38 ppb (Sabel and Clark, 1984). Similarly, the study of Sabel and Clark (1984) reported the detection of 1,2-dichloroethane in 2/6 leachate sites both at a concentration of 5.5 ppb, in 4/13 contaminated groundwater sites at a concentration range of 0.5-240 ppb and in 2/7 uncontaminated groundwaters at trace concentrations. Sabel and Clark (1984) also reported that 1,2-dichloroethane was detected in 2/5 leachate sites in Wisconsin.

From the preceding discussion, it can be concluded that the median concentrations of 1,1- and 1,2-dichloroethane for all United States drinking water supplies sampled are below the detection limit of these compounds. Assuming detection limits for 1,1- and 1,2-dichloroethane as <0.2 and <0.5 μg/ℓ (Westrick et al., 1984), respectively, the maximum individual intake of these compounds as a result of 2 ℓ of drinking water has been estimated to be 0.4 μg/day for 1,1-dichloroethane and 1 μg/day for 1,2-dichloroethane. In instances where these contaminants have been detected in drinking water, the daily intake of these compounds from consumption of such water will be higher. The maximum concentrations of 1,1- and 1,2-dichloroethane reported in any United States water supply are

4.2 and 2100 μg/ℓ, respectively. Combining these concentrations with a value of 2 ℓ of drinking water consumed/day, the maximum 1,1- and 1,2-dichloroethane intake from drinking water for any individual in the United States is estimated to be 8 and 4200 μg/day, respectively.

3.3. FOOD

1,2-Dichloroethane is used as a grain fumigant and therefore is a possible human food contaminant. Because of the volatility of this compound, only negligible amounts remain on food prepared from treated grain (U.S. EPA, 1980). 1,2-Dichloroethane was detected in 11/17 oleoresin spices in concentrations ranging from 2-23 μg/g of spice (U.S. EPA, 1980). Reinert et al. (1983) reported detection of 1,2-dichloroethane up to a maximum concentration of 3.2 mg/kg in killifish, *Fundulus* sp., collected from an unnamed estuary; however, no report regarding the detection of 1,2-dichloroethane in any edible aquatic organism was located in the literature as cited in the Appendix. Entz et al. (1982) analyzed four composite market baskets consisting of dairy products, meats, oils and fats, and beverage products and failed to detect any residue of 1,2-dichloroethane. Bailey et al. (1982) monitored the levels collected in 1979 of fumigant residues in home-produced and imported wheat in England. Of the 61 imported wheat samples analyzed, none showed any detectable residue of 1,2-dichloroethane; however, 1 of the 71 home-grown wheat samples showed a 1,2-dichloroethane level of 290 mg/kg.

Pertinent data regarding residue levels of 1,1-dichloroethane in food products were not located in the available literature cited in the Appendix.

4. PHARMACOKINETICS

4.1. ABSORPTION

Human exposure to dichloroethane is expected to result primarily from inhalation. Ingestion of dichloroethane in contaminated drinking water or in foodstuffs is also a consideration. Dermal absorption of dichloroethane during exposure to the vapor is minimal, but direct contact with the liquid may represent a significant route of exposure in the workplace. Available data pertain primarily to the 1,2-isomer of dichloroethane.

Pulmonary absorption of dichloroethanes is expected to be high based on the high vapor pressure and high blood serum/air partition coefficients (30 for 1,2-dichloroethane, 8 for 1,1-dichloroethane at 25°C) of each isomer (Morgan et al., 1972a,b). In rats, the kinetics of pulmonary absorption of 1,2-dichloroethane was studied by Reitz et al. (1980, 1982) and Spreafico et al. (1980) in 6-hour tests with exposure levels of 50, 150 and 250 ppm (202, 607 and 1012 mg/m^3). Blood levels reached equilibrium within 2 hours at 50 and 150 ppm, while blood levels continued to increase slightly during the interval from 3-6 hours of exposure at 250 ppm. Reitz et al. (1980, 1982) reported that the blood concentration reached a plateau level of 9 μg/mℓ after exposure at 150 ppm (partition coefficient=14.9).

Absorption of 1,2-dichloroethane has been shown to be rapid in rats following oral ingestion (Reitz et al., 1980, 1982; Spreafico et al., 1980) and is assumed to be similarly rapid in other animals and humans. Toxicity studies in animals and reports of accidental or suicidal ingestion of 1,2-dichloroethane in humans (Sections 5.5. and 5.6.) support this supposition. Reitz et al. (1980, 1982) reported complete recovery of radioactivity in exhaled air, urine and carcass following oral administration of ^{14}C-1,2-dichloroethane in corn oil to rats. These data suggest complete gastrointestinal absorption of the compound. Spreafico et al. (1980) reported that absorption of 1,2-dichloroethane (administered at 25, 50 and 150 mg/kg in corn oil) from the gastrointestinal tract was rapid, with peak blood levels reached within 20 minutes of dosing. One-half of the administered dose of 25 mg 1,2-dichloroethane/kg in corn oil was absorbed within 3.3 minutes, and for 150 mg 1,2-dichloroethane/kg in corn oil, 6.4 minutes. Spreafico et al. (1980) reported that gastrointestinal absorption of 1,2-dichloroethane was more rapid when administered in water than corn oil, which is consistent with the lipophilicity of the compound. Withey et al. (1982) confirmed these data by testing the absorption of 1,2-dichloroethane in water or corn oil. Peak blood concentrations were ~5 times higher (84.6 vs. 15.9 μg/mℓ) when the compound (100 mg/kg in 4 mℓ vehicle) was given in water than in corn oil. The time to reach peak blood concentrations was 3.2 minutes for a water solution and 10.6 minutes when 1,2-dichloroethane was administered in corn oil.

Percutaneous absorption of 1,2-dichloroethane following contact with the liquid may represent a significant route of exposure. Tsuruta (1975) measured the percutaneous absorption of 1,2-dichloroethane when applied to the abdominal skin of mice for 15 minutes. Absorption was quantitated by measuring the residue in the body and that in the expired air. The absorption rate for 1,2-dichloroethane was 479 nmol/minute/cm^2 of skin. In vitro, the penetration rate of 1,2-dichloroethane through excised rat skin was 169 nmol/minute/cm^2 of skin (Tsuruta, 1977). Differences noted between the in vivo and in vitro studies may reflect solubility differences of 1,2-dichloroethane in physiological saline vs. the body fluids. Dermal absorption of 1,2-dichloroethane in anesthetized guinea pigs was rapid during the first half hour after treatment (2 mℓ applied to clipped dorsal skin), at which time blood levels rose rapidly, then decreased and finally increased gradually throughout a 12-hour exposure period (Jakobson et al., 1982).

4.2. DISTRIBUTION

Absorbed 1,2-dichloroethane is distributed throughout the body tissues. The compound passes through the blood-brain barrier, causing anesthetic effects, and crosses the placental barrier (U.S. EPA, 1984a). 1,2-Dichloroethane has also been found in breast milk of occupationally exposed women, and remained in the milk for 18 hours following a day's exposure (Urosova, 1953).

In rats, 1,2-dichloroethane absorbed from the gastrointestinal tract passes through the liver, which reaches peak tissue concentrations within 10 minutes (Spreafico et al., 1980). Levels of 1,2-dichloroethane in the liver, kidney and spleen followed levels in the blood. Lung and liver tissue concentrations were less than blood levels (probably due to pulmonary excretion and metabolism of the compound), while adipose tissue levels were 7-17 times levels in the blood. A similar distribution pattern was demonstrated in rats treated by inhalation (Spreafico et al., 1980). After exposure was terminated, blood and tissue levels of 1,2-dichloroethane dropped rapidly (within 1-3 hours) except for adipose tissue, which required ~6 hours to reach baseline levels. Peak blood and tissue levels were dose-dependent by both routes of administration and a 6-hour exposure at 50 ppm (202 mg/m^3) roughly approximated a single 25 mg/kg oral dose.

Due to the rapid elimination of 1,2-dichloroethane, repeated oral exposures at 50 mg/kg (11 consecutive days) did not appear to cause accumulation in the blood or tissues. Adipose tissue levels were similar at 2 hours after a single dose or 2 hours after the eleventh repeated dose, indicating no apparent chronic accumulation.

4.3. METABOLISM

The biotransformation of 1,2-dichloroethane has been studied in rats and mice *in vivo* and *in vitro* using hepatic microsomal preparations. Specific data regarding 1,1-dichloroethane were limited.

Yllner (1971) studied the metabolism of ^{14}C-1,2-dichloroethane in mice following intraperitoneal doses ranging from 50-170 mg/kg. Solvent traps were used to recover urinary and fecal metabolites, and unchanged compound and $^{14}CO_2$ were recovered. At a dose of 50 mg/kg, urinary metabolites, exhaled $^{14}CO_2$ and exhaled unchanged ^{14}C-1,2-dichloroethane accounted for 72.9, 11.9 and 11.0% of the administered dose, respectively. Increased intraperitoneal doses resulted in a smaller percentage of metabolized compound and more unchanged parent compound in the expired air, indicating saturation of the biotransformation capacity. For example, at 170 mg/kg, urinary metabolites, $^{14}CO_2$ and unchanged 1,2-dichloroethane accounted for 50.7, 4.7 and 45.0%, respectively. At all dose levels, ~95% of the radioactive metabolites were recovered during the first 24 hours after injection of the compound. Six urinary metabolites were identified: S-carboxymethylcysteine, thiodiacetic acid, chloroacetic acid, conjugated S-carboxymethylcysteine, S,S'-ethylene-bis-cysteine and 2-chloroethanol, accounting for 45, 33, 16, 3, 0.9 and 0.3% of the urinary radioactivity, respectively.

Metabolism studies of 1,2-dichloroethane following oral and inhalation exposure were conducted by Reitz et al. (1980, 1982) using Osborne-Mendel rats. Rats were treated at 150 mg/kg (single oral dose) or 150 ppm (607 mg/m^3) for 6 hours with ^{14}C-1,2-dichloroethane, and metabolites were measured in the exhaled air, urine and feces, and in the carcass. Following oral administration, 60% of the dose was metabolized and excreted in the urine, while 29 and 5%, respectively, were exhaled as unchanged compound and $^{14}CO_2$. At 48 hours after dosing only 3% remained in the carcass. In the inhalation study (150 ppm for 6 hours), the absorbed dose was estimated to be 50.5 mg/kg based on total recovered radioactivity. Slight differences in pharmacokinetics are apparent, since following inhalation exposure, urinary metabolites, unchanged compound and $^{14}CO_2$ expired in the air accounted for 84, 2 and 7% of the absorbed dose (Reitz et al., 1980, 1982). Two urinary metabolites accounted for almost all radioactivity following oral or inhalation exposure and were identified as thiodiacetic acid and thiodiacetic acid sulfoxide.

Metabolism of 1,2-dichloroethane is proposed to be initiated by hydrolytic dehalogenation yielding 2-chloroethanol (Yllner, 1971). 2-Chloroethanol is expected to be converted to 2-chloroacetic acid by microsomal oxidation. In mice injected intraperitoneally with 1,2-dichloroethane, 2-chloroethanol was a minor metabolite, while chloroacetic acid represented 16% of the urinary metabolites (Yllner, 1971). In a Russian study (Kokarovtseva and Kiseleva, 1978), chloroethanol and chloroacetic acid were reported as metabolites of 1,2-dichloroethane in rats given a single 750 mg/kg oral dose. In vitro, the percent of available ^{36}Cl removed from ^{36}Cl-1,1- and ^{36}Cl-1,2-dichloroethane was 13.5 and <0.5%, respectively (Loew et al., 1973). Salmon et al. (1981) also indicated that 1,1-dichloroethane is dechlorinated more rapidly than the 1,2-isomer. The values of V_{max} obtained in vitro with hepatic microsomal preparations were 41.7 and 0.24 nmol/min/mg protein, respectively, for 1,1- and 1,2-dichloroethane. McCall et al. (1983) examined the metabolism of 1,1- and 1,2-dichloroethane in vitro by hepatic microsomes from phenobarbital-induced rats. In the presence of an NADPH-generating system, metabolites of 1,1-dichloroethane included acetic acid (179 nmol/mg microsomal protein/20 minutes), chloroacetic acid (0.22 nmol/mg protein/20 minutes), 2,2-dichloroethanol (0.12 nmol/mg protein/20 minutes) and trace amounts of dichloroacetic acid and chloroacetaldehyde. 1,2-Dichloroethane was metabolized to chloroacetaldehyde (35 nmol/mg protein/20 min), chloroacetic acid (0.31 nmol/mg protein/20 min) and 2-chloroethanol (0.20 nmol/mg protein/20 min). These data also suggest that 1,1-dichloroethane is more rapidly dechlorinated and metabolized than the 1,2-isomer. The proposed metabolic pathways of 1,1-dichloroethane are shown in Figure 4-1.

Casciola and Ivanetich (1984) reported that 1,2-dichloroethane was metabolized primarily to chloroacetaldehyde by hepatic microsomal cytochrome P-450 and hepatic nuclear cytochrome P-450. Guengerich et al. (1980) proposed that microsomal cytochrome P-450, in the presence of O_2 and NADPH, metabolized 1,2-dichloroethane by oxygen insertion to an unstable chlorohydrin, which spontaneously dechlorinates to form 2-chloroacetaldehyde. Chloroacetaldehyde is reduced by alcohol dehydrogenase (with NADH) to chloroethanol or further oxidized to chloroacetic acid. Guengerich et al. (1980) also proposed the formation of 1-chloroso-2-chloroethane by mixed function oxidase. This reactive intermediate may undergo spontaneous dechlorination, forming 2-chloroethanol or 2-chloroacetaldehyde. 1-Chloroso-2-chloroethane is also susceptible to thiol attack and conjugation with glutathione, leading to an episulfonium ion which may attach to cellular macromolecules. The reactive 1-chloroso-2-chloroethane molecule itself may react directly with cellular macromolecules.

Livesey and Anders (1979) and Anders and Livesey (1980) showed _in vitro_ that 1,2-dichloroethane can be conjugated directly with glutathione, which

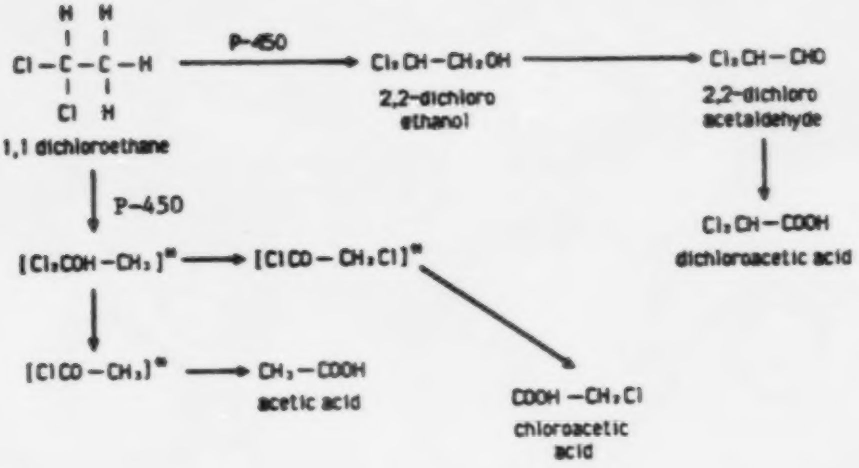

P-450
Cl–C–C–H
1,1 dichloroethane
Cl₂CH–CH₂OH
2,2-dichloro ethanol
Cl₂CH–CHO
2,2-dichloro acetaldehyde
Cl₂CH–COOH
dichloroacetic acid
P-450
[Cl₂COH–CH₃]*
[ClCO–CH₂Cl]*
[ClCO–CH₃]*
CH₃–COOH
acetic acid
COOH–CH₂Cl
chloroacetic acid

FIGURE 4-1

Proposed Metabolic Pathways of 1,1-Dichloroethane

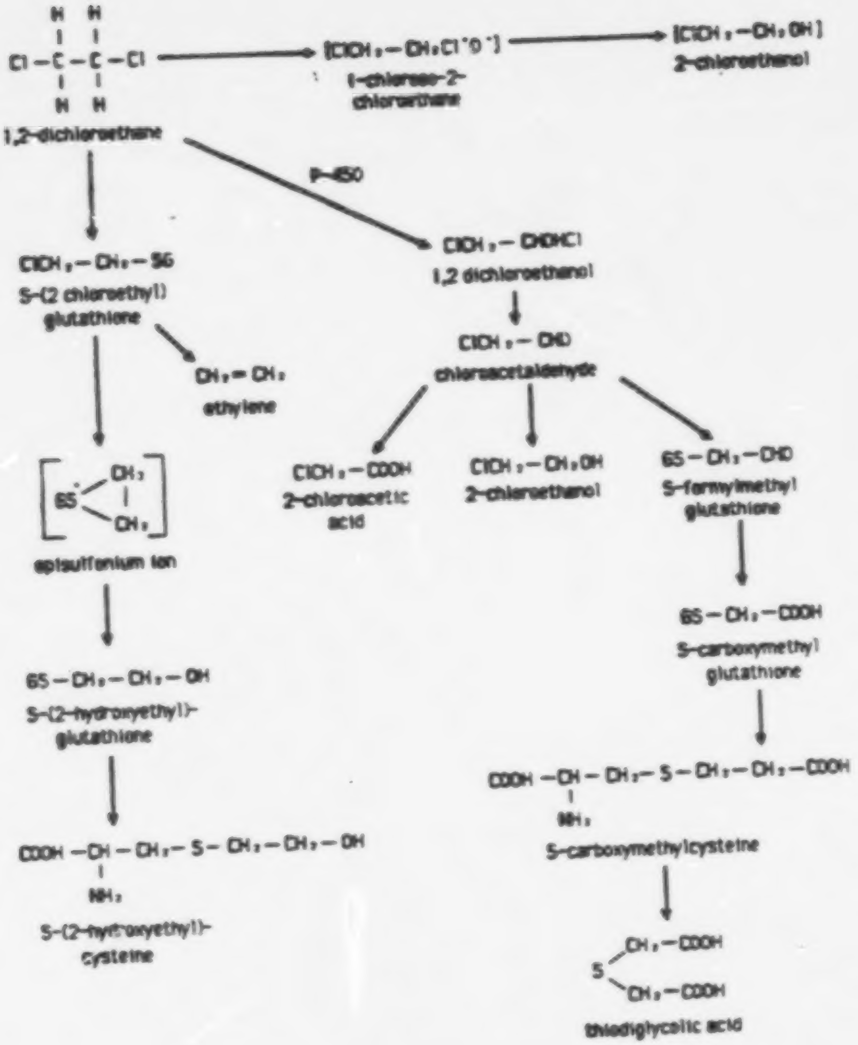
Source: McCall et al., 1983; Loew et al., 1984

*Brackets indicate unstable intermediate metabolites removes a chloride ion. The presumed intermediate, S-(2-chloroethyl) glutathione, may be attacked by a thiol group (since the presence of sulfhydryl compounds is necessary), causing secondary dehalogenation and the formation of a disulfide (glutathione and thiol-attacking compound). The end product of 1,2-dichloroethane would be ethylene by this metabolic pathway which requires reduced glutathione. Dechlorination of S-(2-chloroethyl) glutathione could also lead to formation of an episulfonium ion, which could further react with glutathione or water to yield S,S-ethylene-bis-glutathione or S-(2-hydroxy-ethyl)-glutathione (U.S. EPA, 1984a). Albano et al. (1984) demonstrated the depletion of hepatic glutathione by 1,2-dichloroethane in vitro. Johnson (1966a,b; 1967) suggested that the conjugation of chloroacetaldehyde with glutathione represents a major detoxification pathway. In vitro, this conjugation proceeded by a non-enzymatic process, yielding S-carboxymethyl-glutathione. This compound degraded to yield glycine, glutamic acid and S-carboxymethylcysteine. S-Carboxymethylcysteine may be further oxidized to thiodiglycolic acid. Both S-carboxymethylcysteine and thiodiglycolic acid were found as urinary metabolites in rats and mice given 1,2-dichloroethane in vivo (Yllner, 1971; Spreafico et al., 1980).

A summary of some of the proposed metabolic pathways of 1,2-dichloroethane is presented in Figure 4-2. These pathways have been primarily elucidated using in vitro hepatic microsomal systems, but appear consistent with metabolites detected in vivo.

4.4. EXCRETION

Elimination of 1,2-dichloroethane and its metabolites occurs primarily by urinary excretion or exhalation by the lungs. Carbon dioxide and unchanged parent compound are excreted by the lungs, while most of the



Cl-C-C-Cl
1,2-dichloroethane
[ClCH2-CH2Cl+O-]
1-chloroso-2-chloroethane
[ClCH2-CH2OH]
2-chloroethanol
P-450
ClCH2-CH2-SG
S-(2 chloroethyl) glutathione
ClCH2-CHOHCl
1,2 dichloroethanol
ClCH2-CHO
chloroacetaldehyde
CH2=CH2
ethylene
GS CH2 CH2
episulfonium ion
ClCH2-COOH
2-chloroacetic acid
ClCH2-CH2OH
2-chloroethanol
GS-CH2-CHO
S-formylmethyl glutathione
GS-CH2-COOH
S-carboxymethyl glutathione
GS-CH2-CH2-OH
S-(2-hydroxyethyl)-glutathione
COOH-CH-CH2-S-CH2-CH2-COOH
NH2
S-carboxymethylcysteine
COOH-CH-CH2-S-CH2-CH2-OH
NH2
S-(2-hydroxyethyl)-cysteine
S CH2-COOH CH2-COOH
thiodiglycolic acid

FIGURE 4-2

Proposed Metabolic Pathways of 1,2-Dichloroethane

Source: U.S. EPA, 1984a; Loew et al., 1984 absorbed compound (at low doses) is eliminated as metabolites in urine. In mice injected intraperitoneally with 1,2-dichloroethane at 50, 100, 140 and 170 mg/kg, unchanged compound expired in the air accounted for 11.0, 20.6, 46.1 and 45.0% of the administered dose, respectively (Yllner, 1971). Carbon dioxide accounted for 11.9, 8.2, 4.3 and 4.7%, respectively, at the four dose levels. Excretion of urinary metabolites accounted for 72.9, 71.7, 48.6 and 50.7% of the respective doses. Due to the rapid metabolism of 1,2-dichloroethane, elimination was ~95% complete within 24 hours of dosing at all dose levels.

Following oral dosing with 1,2-dichloroethane at 150 mg/kg, pulmonary exhalation of unchanged compound accounted for 29% of the administered dose (Reitz et al., 1980, 1982). Carbon dioxide and urinary metabolites represented 5.4 and 60.2%, respectively. Reitz et al. (1980, 1982) also reported the excretion of 1,2-dichloroethane and metabolites following inhalation exposure at 150 ppm (607 mg/m^3) for 6 hours (estimated ~50 mg/kg absorbed dose). Exhalation of unchanged parent compound was only 1.8%, while carbon dioxide and urinary metabolites accounted for 7.1 and 84.4%, respectively, of the absorbed dose. Fecal excretion by either route was <2%, which may represent biliary metabolites. Elimination was 96% complete within 48 hours.

The kinetics of excretion of 1,2-dichloroethane has been studied in the rat following intravenous (Withey and Collins, 1980; Spreafico et al., 1980), oral (Spreafico et al., 1980; Reitz et al., 1982) and inhalation exposure (Spreafico et al., 1980; Reitz et al., 1980, 1982). Following intravenous exposure at low doses (3 and 6 mg/kg), elimination from blood in rats exhibited a first-order kinetics consistent with a two-compartment model (Withey and Collins, 1980). At higher doses (9, 10, 15 mg/kg), blood decay curves best fit a first-order, three-compartment model. Withey and

Collins (1980) suggested that the third compartment kinetics may have resulted in dose-related changes in distribution or metabolism, or that at low doses the third compartment was obscured by the limit of analytical sensitivity. Spreafico et al. (1980) reported that a two-compartment model represented 1,2-dichloroethane excretion in rats. These investigators noted that the half-time of total body elimination increased with dose (1, 5 and 25 mg/kg), and the rate was determined by the metabolic rate of 1,2-dichloroethane.

The kinetics observed following oral dosing in rats is similar to that determined after intravenous exposure. A two-compartment model best fitted the blood and body elimination data (Spreafico et al., 1980). The kinetic parameters were dose-dependent but were no different after 11 daily doses (50 mg/kg) than after a single dose. Administration of 1,2-dichloroethane in water, as compared with oil, resulted in more rapid absorption and shorter half-times of elimination. Reitz et al. (1980, 1982) reported a two-compartment model of elimination for a 150 mg/kg oral dose in corn oil. The initial elimination phase appeared to have a half-time of ~90 minutes, but elimination became more rapid when blood levels of 1,2-dichloroethane fell to 5-10 μg/mℓ and had a secondary half-time of ~20-30 minutes.

The kinetics of excretion of 1,2-dichloroethane following inhalation exposure was studied by Spreafico et al. (1980). Rats were exposed at 50 and 250 ppm (202 and 1012 mg/m^3) for 5 hours, and blood and tissue samples were taken to determine elimination of 1,2-dichloroethane. In contrast to intravenous or oral dosing studies, the elimination of 1,2-dichloroethane by rats exposed via inhalation was determined to be monophasic; elimination was studied after inhalation of the compound was terminated. The authors suggested that biphasic curves reported after oral and intravenous exposure represented an adsorption-distribution phase and an elimination phase, and that these inhalation studies measured only the elimination phase. The reported half-times of elimination following exposure at 50 and 250 ppm for 5 hours were 12.69 and 22.13 minutes, respectively. The elimination of 1,2-dichloroethane was dose-related, presumably due to the saturable process of metabolism.

Specific data regarding the excretion of 1,1-dichloroethane and its metabolites were not located in the available literature cited in the Appendix. Based on the in vitro metabolism studies by Salmon et al. (1981) and McCall et al. (1983), 1,1-dichloroethane appears to be more rapidly metabolized (dechlorinated) than the 1,2-isomer. The elimination of 1,1-dichloroethane may proceed more rapidly than that of 1,2-dichloroethane.

5. EFFECTS

5.1. CARCINOGENICITY

In reviews of the carcinogenicity data on 1,2-dichloroethane, Fishbein (1979) and Infante and Marlow (1980) reported that up to 2 million workers may be exposed to this chemical, but few data are available on the effects of chronic occupational exposure. Austin and Schnatter (1983) conducted a case-control study of brain tumors in petrochemical workers, but found no association between exposure to 1,2-dichloroethane and cancer.

In animals, several carcinogenicity studies have been conducted on 1,2-dichloroethane using oral (NCI, 1978a; Weisburger, 1977; Ward, 1980), inhalation (Maltoni et al., 1980, 1982), dermal (Van Duuren et al., 1979) and intraperitoneal administration (Theiss et al., 1977). The carcinogenicity of 1,1-dichloroethane administered by gavage was tested in a bioassay using mice and rats (NCI, 1978b; Weisburger, 1977).

The carcinogenicity bioassay of 1,2-dichloroethane sponsored by the NCI (1978a) was conducted using Osborne-Mendel rats and B6C3F1 mice. The compound was administered in corn oil by gavage at two dose levels to groups of 50 animals of each sex and species. Groups of 20 animals of each sex and species were maintained as untreated controls, while similar groups of 20 were given corn oil only. Initial dose levels given to rats were 50 and 100 mg/kg/day, but doses were increased and decreased during the 78-week dosing period so that TWA dose levels were 47 and 95 mg/kg/day. Doses were administered on 5 days/week for 78 weeks, followed by an observation period of 15-32 weeks. Male mice were treated at 75 or 150 mg/kg/day on 5 days/week for 8 weeks, at which time dose levels were increased to 100 and 200 mg/kg/day for 70 additional weeks. The TWA doses were 97 and 195 mg/kg/day on 5 days/week for 78 weeks, followed by 12-13 weeks of observation. Female mice were treated at 149 and 299 mg/kg/day on 5 days/week as a TWA for 78 weeks. An observation period of 13 weeks of non-exposure was allowed prior to the terminal sacrifice of survivors.

Among the high dose group rats of both sexes, mortality was high because of toxic effects and bronchopneumonia. At 55-57 weeks of treatment, 50% of high dose males (25/50) and females (25/50) had died; none survived until the terminal sacrifice period. Low dose rats also had decreased survival, with only 1/50 of each sex surviving until the end of the study, while 20-65% of the vehicle and untreated control rats survived until terminal sacrifice. Survival in the mice was similar among dose groups and controls except in high dose females, which had 1/50 survivors at 91 weeks.

Gross and histopathological examinations were performed on all available animals. Tissues from 28 organs and all visible lesions were examined microscopically for each animal. Squamous cell carcinoma of the forestomach occurred in treated male rats, with the first observed lesions occurring at 51 weeks. Carcinomas extended into the epithelium, muscularis mucosa, submucosa, muscular layers and serosal layers. The incidence of forestomach carcinomas was significantly ($p=0.007$) increased in the high dose group and showed a significant ($p=0.001$) dose-related trend (9/50 in high dose males, 3/50 in low dose males, 0/60 among pooled controls) (Table 5-1). Significantly increased incidences of hemangiosarcomas of the circulatory system and subcutaneous fibromas also showed a significant dose-related trend among male rats receiving 1,2-dichloroethane (see Table 5-1). Female rats treated with 1,2-dichloroethane developed mammary gland fibroadenomas and adenocarcinomas at a significantly ($p<0.01$) higher incidence than control rats. The incidence for combined mammary fibromas and adenocarcinomas was 24/50, 15/50 and 6/59, respectively, for high dose, low dose and pooled control females (see Table 5-1).

TABLE 5-1

Oral Gavage Studies for 1,2-Dichloroethane[a]

Species/ Strain	Sex	Dose	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence[b] (p value)
Rats/ Osborne-Mendel	M	95 mg/kg[c]	78	101	≥99%[d]	corn oil	forestomach	squamous cell carcinoma	9/50 (p=0.007)[e]
							circulatory system	hemangiosarcoma	7/50 (p=0.016)[e]
							subcutaneous tissue	fibroma	6/50 (p=0.001)[e] (p=0.039)[f]
Rats/ Osborne-Mendel	M	47 mg/kg[c]	78	110	≥99%[d]	corn oil	forestomach	squamous cell carcinoma	3/50 (NS)
							circulatory system	hemangiosarcoma	9/50 (p=0.003)[e] (p=0.039)[f]
							subcutaneous tissue	fibroma	5/50 (p=0.017)[e]
Rats/ Osborne-Mendel	M	0 mg/kg/day (matched vehicle control)	78	110	NA	corn oil	forestomach	squamous cell carcinoma	0/20 (p=0.010)
							circulatory system	hemangiosarcoma	0/20 (NS)
							subcutaneous tissue	fibroma	0/20 (NS)
Rats/ Osborne-Mendel	M	0 mg/kg/day (pooled vehicle control)[g]	≥52	≥52	NA	corn oil	forestomach	squamous cell carcinoma	0/60 (p=0.001)
							circulatory system	hemangiosarcoma	1/60 (p=0.021)
							subcutaneous tissue	fibroma	0/60 (p=0.010)

TABLE 5-1 (cont.)

Species/ Strain	Sex	Dose	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence[b] (p value)
Rats/ Osborne-Mendel	F	95 mg/kg[c]	78	93	≥99%	corn oil	mammary gland	adenocarcinoma NOS	18/50 (p<0.001)[e] (p=0.002)[f]
							mammary gland	adenocarcinoma NOS or fibroadenoma	24/50 (p<0.001)[d,e]
Rats/ Osborne-Mendel	F	47 mg/kg[c]	78	110	≥99%	corn oil	mammary gland	adenocarcinoma NOS	1/50 (NS)
							mammary gland	adenocarcinoma NOS or fibroadenoma	15/50 (p=0.009)[e] (p=0.003)[f]
Rats/ Osborne-Mendel	F	0 mg/kg (matched vehicle control)	78	110	NA	corn oil	mammary gland	adenocarcinoma NOS	0/20 (p<0.001)
							mammary gland	adenocarcinoma NOS or fibroadenoma	0/20 (p<0.001)
Rats/ Osborne-Mendel	F	0 mg/kg (pooled vehicle control)[g]	≥52	≥52	NA	corn oil	mammary gland	adenocarcinoma NOS	1/59 (p<0.001)
							mammary gland	adenocarcinoma NOS or fibroadenoma	6/59 (p<0.001)
Mice/ B6C3F1	M	195 mg/kg[c]	78	91	≥99%	corn oil	lung	alveolar/bronchiolar adenoma	15/48 (p<0.001)[e] (p=0.003)[f]
							liver	hepatocellular carcinoma	12/48 (p=0.009)[e]
Mice/ B6C3F1	M	97 mg/kg[c]	78	90	≥99%	corn oil	lung	alveolar/bronchiolar adenoma	1/47 (NS)
							liver	hepatocellular carcinoma	6/47 (NS)

TABLE 5-1 (cont.)

Species/ Strain	Sex	Dose	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence[b] (p value)
Mice/ B6C3F1	M	0 mg/kg (matched vehicle controls)	78	90	NA	corn oil	lung	alveolar/bronchiolar adenoma	0/19 ($p<0.001$)
							liver	hepatocellular carcinoma	1/19 ($p=0.025$)
Mice/ B6C3F1	M	0/mg/kg (pooled vehicle controls)	≥52	≥52	NA	corn oil	lung	alveolar/bronchiolar adenoma	0/59 ($p<0.001$)
							liver	hepatocellular carcinoma	4/59 ($p=0.006$)[f]
Mice/ B6C3F1	F	299 mg/kg[c]	78	91	≥99%	corn oil	lung	alveolar/bronchiolar adenoma	15/48 ($p<0.001$)[e] ($p=0.006$)[f]
							mammary gland	adenocarcinoma	7/48 ($p=0.003$)[e]
							uterus	endometrial stromal polyp or sarcoma	5/47 ($p=0.014$)[e]
Mice/ B6C3F1	F	149 mg/kg[c]	78	91	≥99%	corn oil	lung	alveolar/bronchiolar adenoma	7/50 ($p=0.046$)[e]
							mammary gland	adenocarcinoma	9/50 ($p=0.001$)[e] ($p=0.039$)[f]
							uterus	endometrial stromal polyp or sarcoma	5/49 ($p=0.016$)
Mice/ B6C3F1	F	0 mg/kg (matched vehicle controls)	78	90	NA	corn oil	lung	alveolar/bronchiolar adenoma	1/20 ($p=0.005$)
							mammary gland	adenocarcinoma	0/20 (NS)
Mice/ B6C3F1	F	0 mg/kg (matched vehicle controls)	78	90	NA	corn oil	uterus	endometrial stromal polyp or sarcoma	0/20 (NS)

TABLE 5-1 (cont.)

Species/ Strain	Sex	Dose	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence[b] (p value)
Mice/ B6C3F1	F	0 mg/kg (pooled vehicle controls)	≥52	≥52	NA	corn oil	lung	alveolar/bronchiolar adenoma	2/60 $p<0.001$)
							mammary gland	adenocarcinoma	0/60 ($p=0.007$)
							uterus	endometrial stromal polyp or sarcoma	0/60 $p=0.017$)

QUALITY OF EVIDENCE

Strengths of study: The compound was administered by a natural route at two dose levels for a significant portion of the lifespan. Two dose levels were employed and complete histopathological examinations were performed. The study was conducted in both sexes of two species using a large number of animals in each group.

Weakness of Study: Elevated mortality was associated with the high dose treatment in both male and female rats and in female mice.

Overall Adequacy: Adequate

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[a] Source: NCI, 1978a

[b] The probability levels for the Fischer exact test and Cochran-Armitage test are given beneath the incidence of tumors in the treated and control groups, respectively, when $p<0.05$; otherwise, not significant (NS) is indicated.

[c] TWA dose reflecting gavage treatment 5 consecutive days/week for 78 weeks.

[d] Purity of >90% was reported by NCI (1978a). Reanalysis indicated a purity of ≥99% (Hooper et al., 1980).

[e] Comparison with pooled control group.

[f] Comparison with matched control group.

[g] Pooled control group consisted of matched controls from bioassays of 1,2-dichloroethane, 1,1,2-trichloroethane and trichloroethylene.

NA - Not applicable; NOS - not otherwise specified

In male mice, histopathological examinations revealed an increase in hepatocellular carcinoma and alveolar-bronchiolar adenoma among treated groups compared to controls. The incidence of hepatocellular carcinoma was 12/48 (p=0.009) and 6/47 (not significant) in high dose and low dose groups, respectively, while the incidences in matched and pooled vehicle control groups were 1/19 and 4/59. Alveolar-bronchiolar adenomas occurred in 15/48 (p<0.001), 1/47 (not significant), 0/19 and 0/59 among high dose, low dose, matched and pooled vehicle control groups, respectively (see Table 5-1). Female mice also developed an increased incidence of alveolar and bronchiolar adenomas with incidences of 15/48, 7/50, 1/20 and 2/60 in high dose, low dose, matched and pooled vehicle control groups, respectively. Mammary gland adenocarcinoma and endometrial polyps or sarcoma occurred in 7/48 (p=0.003) and 5/47 (p=0.014) females in the high dose group and 9/50 (p=0.001) and 5/49 (p=0.016) mice in the low dose group, while no tumors of these types occurred in matched (0/20) or pooled vehicle control groups (0/60) (see Table 5-1).

The carcinogenicity of 1,2-dichloroethane following inhalation was examined in a bioassay conducted by (Maltoni et al., 1980) in Spraque-Dawley rats and Swiss mice. Four groups of 90 animals of each sex and species were initially exposed to 1,2-dichloroethane at 5, 10, 50 and 250 ppm (20, 40, 202 and 1012 mg/m^3) for 7 hours/day, 5 days/weeks. Due to toxic effects in rats and mice exposed at 250 ppm, this exposure level was reduced to 150 ppm (607 mg/m^3) after exposure for 10 weeks in rats and several days in mice. All exposures were continued for 78 weeks and animals were subsequently maintained for their lifetime. Air-exposed controls (in exposure chambers) and untreated controls, each group containing 90 animals of each sex and species, were maintained for comparison. Complete necropsy and histopathological examination of major organs and tissues were performed on each animal. Mortality among treated animals did not appear to be related to exposure to 1,2-dichloroethane. Histopathological examinations revealed no statistically significant increase in any type of tumor among treated rats or mice compared with controls (Table 5-2). Female rats exposed at 5, 50 and 250 to 150 ppm had an increased incidence of mammary gland fibromas and fibroadenomas (non-malignant) compared with air-exposed controls, but not when compared with unexposed controls. The development of mammary tumors in rats is age-related and incidence rates were attributed to different survival rates of the groups. Maltoni et al. (1982) reported on the incidence of brain tumors among rats exposed by inhalation to 5, 10, 50 and 250 reduced to 150 ppm. Brain tumors, classified as ependymonas, gliomas or meningiomas, were rare among all groups (treated and controls) and could not be attributed to 1,2-dichloroethane exposure. In fact, no brain tumors occurred among rats of the high dose group; the controls had the highest incidence (5/360).

The carcinogenicity and initiating activity of 1,2-dichloroethane on the skin was tested by Van Duuren et al. (1979) in female ICR/Ha Swiss mice. In the complete carcinogen test, 126 mg 1,2-dichloroethane in acetone was applied to the dorsal skin of 30 mice 3 times/week for 440-594 days (exact duration not specified). None of the mice treated repeatedly developed skin tumors, but benign pulmonary papillomas developed in 26/30 mice and forestomach papillomas and carcinomas occurred in 3/30 and 2/30 mice, respectively. The incidence of lung tumors was significantly increased compared with vehicle (11/30) and untreated controls (30/100). Forestomach tumors were not significantly increased compared with controls. In the initiation studies, one application of 126 mg 1,2-dichloroethene in acetone was placed

TABLE 5-2

Bioassay Results for 1,2-Dichloroethane Administered by Inhalation for 78 Weeks[a]

Species/ Strain	Sex	Dose	Duration of Study	Purity of Compound (%)	Vehicle or Physical State	Tumor Type
Rats/ Sprague-Dawley	M/F[b]	250 to 150[c], 50, 10, 5 or 0[d] ppm; 7 hours/day, 5 days/week	life	99.82	vapor	Significant treatment-related increases in the incidence of any specific type of tumor were not observed.[e]
Mice/ Swiss	M/F[f]	250 to 150[c] 50, 10, 5, or 0 ppm 7 hours/day, 5 days/week	life	99.82	vapor	Significant treatment-related increases in the incidence of any specific type of tumor were not observed.[e]

QUALITY OF EVIDENCE

Strengths of study: The compound was administered by a natural route for a significant portion of the lifespan, and the animals were observed for life. Four treatment levels were employed and complete histopathological examinations were performed. The study was conducted in both sexes of two species using a large number of animals in each group.

Overall Adequacy: Adequate

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[a] Source: Maltoni et al., 1980

[b] 90 rats/sex/dose tested

[c] After 10 weeks of 250 ppm exposure, the concentration was reduced to 150 ppm due to high toxicity.

[d] Both chamber control and outside control groups were used.

[e] A significant increase in the incidence of mammary fibromas and fibroadenomas was observed in the 250 to 150, 50 and 5 ppm female rats when compared with chamber but not outside controls, and was attributed primarily to the different survival rates of the groups (the onset of these tumors is age-correlated).

[f] 90 mice/sex/dose tested except 0 ppm (115 males, 134 females)

on the dorsal skin of 30 mice, followed 14 days later by 5 µg of PMA as the promoter, 3 times/week for 428-576 days. The incidence of skin tumors was not increased compared with controls; therefore, 1,2-dichloroethane was not regarded as an initiator.

Using the development of lung adenomas in Strain A mice as an indicator of carcinogenic activity, Theiss et al. (1977) reported that mice treated with 1,2-dichloroethane developed more pulmonary tumors than vehicle controls in a dose-related manner, but increased incidences were not significant. 1,2-Dichloroethane was administered by intraperitoneal injection at 20, 40 and 100 mg/kg, 3 times/week for 6 weeks. Mice were sacrificed for microscopic examination at 24 weeks after the first injection. The number of tumors/mouse was 0.39, 0.21, 0.44 and 0.75 ($p=0.097$) for vehicle-control, low, middle and high dose groups, respectively.

The carcinogenicity of 1,1-dichloroethane was tested by the NCI (1978b) in a chronic bioassay using Osborne-Mendel rats and B6C3F1 mice. Technical grade 1,1-dichloroethane was administered by gavage in corn oil to groups of 50 animals of each sex and species at two dose levels on 5 days/week for 78 weeks. Following the exposure period, an observation period of 33 weeks for rats and 13 weeks for mice was allowed prior to sacrifice and complete necropsy of all surviving animals. Due to adjustments in the dosage during the study, high and low dose TWAs (for 5 days/week) were 764 and 382 mg/kg/day for male rats; 950 and 475 mg/kg/day for female rats; 2885 and 1442 mg/kg/day for male mice and 3331 and 1665 mg/kg/day for female mice. Control groups consisted of 20 animals of each sex and species exposed to the vehicle (corn oil) and untreated (not intubated). Survival among all rat groups and male mice groups was poor. In all treated groups of rats and mice there was a positive association between treatment and mortality.

Pneumonia was the major cause of death in the rats. After gross and histopathological analysis of major tissues, organs and gross lesions, no significant increase in neoplasms was evident in treated male or female rats compared with control groups (Table 5-3). Adenocarcinoma of the mammary gland occurred in 5/50, 1/50, 0/19 and 1/20 female rats in the high dose, low dose, vehicle controls and untreated control groups, respectively, but the incidence among high dose females was not significantly different from control. When analysis was performed upon female rats surviving for 52 weeks, the Cochran-Armitage test showed a significant (p=0.034) positive association between 1,1-dichloroethane treatment and development of mammary gland adenocarcinoma. The incidence of 4/50 hemangiosarcomas (two subcutaneous, one pulmonary, one splenic) in the high dose female rats was significantly (p=0.04) increased compared to vehicle controls (see Table 5-3).

Histopathological examination of male mice revealed an increase (not significant) in the incidence of hepatocellular carcinoma among treated groups. The incidence of hepatocellular carcinoma was 8/47, 8/49, 1/19 and 2/17 in high dose, low dose, vehicle control and untreated control groups, respectively (see Table 5-3). Neoplasms among female mice were relatively few. Uterine endometrial stromal polyps (benign tumors) were identified in 4/46 (p=0.017) females of the high dose group, while none were observed in any other group. Two lymphomas of the cervical lymph node were detected among female mice of the high dose group, with no tumors of this type occurring in females of other groups (see Table 5-3).

The NCI (1978b) concluded that the high mortality rate of both species precluded the appearance of possible late-developing tumors. Despite the poor survival, the positive correlation between dosage and incidence of mammary adenocarcinomas in female rats was suggestive of carcinogenicity of

TABLE 5-3

Oral Gavage Studies for 1,1-Dichloroethane[a]

Species/ Strain	Sex	Dose[b] (mg/kg/day)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound (%)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Rat/ Osborne-Mendel	M	764	78	111	>99	corn oil	pituitary	chromophobe adenoma	2/46 (NS)
	M	382	78	111	>99	corn oil	pituitary	chromophobe adenoma	0/44
	M	0.0	78	111	NA	corn oil	pituitary	chromophobe adenoma	1/20
	M	0.0	NA	111	NA	none	pituitary	chromophobe adenoma	0/19
Rat/ Osborne-Mendel	F	950	78	111	>99	corn oil	mammary gland circulatory system	adenocarcinoma hemangiosarcoma	5/50 (NS) 4/50 (p=0.04)
	F	475	78	111	>99	corn oil	mammary gland circulatory system	adenocarcinoma hemangiosarcoma	1/50 0/50
	F	0.0	78	111	NA	corn oil	mammary gland circulatory system	adenocarcinoma hemangiosarcoma	0/19 0/19
	F	0.0	NA	111	NA	none	mammary gland circulatory system	adenocarcinoma hemangiosarcoma	1/20 0/20
Mice/ B6C3F1	M	2885	78	91	>99	corn oil	lung; liver	adenoma; hepatocellular carcinoma	4/47 (NS) 8/47 (NS)
	M	1442	78	91	>99	corn oil	lung; liver	adenoma; hepatocellular carcinoma	1/49 8/49
	M	0.0	78	91	NA	corn oil	lung; liver	adenoma; hepatocellular carcinoma	0/19 1/19
	M	0.0	NA	91	NA	none	lung; liver	adenoma; hepatocellular carcinoma	0/17 2/17

TABLE 5-3 (cont.)

Species/ Strain	Sex	Dose[b] (mg/kg/day)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound (%)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Mice/ B6C3F1	F	3331	78	91	>99	corn oil	uterus; cervical lymph node	stromal polyp lymphoma	4/46 (p=0.017) 2/47 (NS)
	F	1665	78	91	>99	corn oil	uterus; cervical lymph node	stromal polyp lymphoma	0/46 0/47
	F	0.0	78	91	NA	corn oil	uterus; cervical lymph node	stromal polyp lymphoma	0/46 0/47
	F	0.0	NA	91	NA	none	uterus; cervical lymph node	stromal polyp lymphoma	0/46 0/47

QUALITY OF EVIDENCE

Strengths of study: Two species of animals were tested using both sexes exposed at two dose levels. A natural route of administration was used. The duration of treatment and study was sufficient. Histopathological examinations of major tissues/organs were performed. The study was conducted in both sexes of two species using a large number of animals in each group.

Weakness of Study: Early mortality prevented adequate testing of possible late-developing neoplasms.

Overall Adequacy: Adequate

Comment: No conclusive evidence of carcinogenicity of 1,1-dichloroethane was demonstrated.

[a]Source: NCI, 1978b

[b]Time-weighted average dosage administered on 5 days/week

NA = Not applicable; NS = not stated

1,1-dichloroethane. There was also a significant dose-related increase in the incidence of hemangiosarcomas at various sites among female rats. Only the incidence of benign endometrial polyps was increased in dosed female mice. This bioassay, therefore, suggests possible evidence for carcinogenicity of 1,1-dichloroethane in Osborne-Mendel rats or B6C3F1 mice.

5.2. MUTAGENICITY

5.2.1. 1,2-Dichloroethane. The mutagenic activity of 1,2-dichloroethane has been tested in bacteria, plants, *Drosophila melanogaster*, mammalian cells *in vitro* and in *in vivo* rodent assays. A number of authors have reviewed 1,2-dichloroethane mutagenicity data (Fishbein, 1979; Rannug, 1980; Simmon, 1981; U.S. EPA, 1984a).

In bacterial assay systems, 1,2-dichloroethane has generally elicited marginally positive mutagenesis without metabolic activation and stronger mutagenic responses when exogenous metabolic systems were added. Representative data regarding the mutagenicity of 1,2-dichloroethane in microbial assay systems are summarized in Table 5-4. The most sensitive strain of *Salmonella typhimurium* was TA1535, in which positive results were obtained in many tests while other strains showed no reverse mutation.

Studies conducted by Rannug (1976), Rannug and Ramel (1977), Rannug et al. (1978) and Rannug and Beije (1979) were conducted to test the mutagenic activity of 1,2-dichloroethane as a direct-acting mutagen and its metabolites. In *S. typhimurium* TA1535, 1,2-dichloroethane with no activation system or other supplementation elicited a 2-fold increase in revertants (24.8 vs. 13.0 background). When a metabolic activation system was provided, a 10-fold increase in revertants occurred (132.8 vs. 15.5 revertants/plate). Subsequent tests (Rannug et al., 1978) were performed, varying the components of the activation system: with and without an NADPH-generating

TABLE 5-4

Summary of Mutagenicity Data of 1,2-Dichloroethane in Microbial Assays

Assay	Indicator/ Organism	Compound/ Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse gene mutation	Salmonella typhimurium	NR	spot test	10 μmol/disk	none	weakly positive in TA1530, TA1535; negative in TA1538	Volatility prevented plate incorporation	Brem et al., 1974
Reverse gene mutation	S. typhimurium	NR	spot test	10 μmol/disk	none	weakly positive in TA1535	--	Rannug et al., 1978
					S-9	positive in TA1535	Activation caused by conjugation with glutathione	
Reverse gene mutation	S. typhimurium	98.5	spot test	0.1 mℓ of liver perfusate	isolated perfused liver	positive	24 μmol perfused to liver	Rannug and Beije, 1979
			plate test	0.1 mℓ of bile	isolated perfused liver	positive	24 μmol perfused to liver	
Reverse gene mutation	S. typhimurium	NR	plate test	36 μmol/plate	PCB-induced rat liver S-9	negative	Negative results in TA1535, TA1537, TA1538, TA100, TA98	King et al., 1979
Reverse gene mutation	S. typhimurium	NR	plate test	10 mg/plate	Aroclor 1254 induced rat liver S-9	negative	Strains TA1535, TA1537, TA1538, TA100, TA98	Nestmann et al., 1980
			plate test in dessicator	10 mg/plate	±	slightly positive in TA1535 and TA100	Dessicator prevented evaporative loss of volatile compounds	
Reverse gene mutation	S. typhimurium	99%	plate test	10 μmol/plate	±; PCB-induced rat liver S-9	negative	Tested in TA100; toxic effects produced at higher test levels	Stolzenberg and Hine, 1980
Reverse gene mutation	S. typhimurium	NR	spot test	100 μℓ/plate	±S-9	positive in TA1535	Negative in TA1537, TA1538 TA98, TA100; no precautions were taken to prevent evaporative loss	Principe et al., 1981
Reverse gene mutation	S. typhimurium	NR	spot test	100 μℓ/plate	±S-9	positive in TA1535	Negative in TA1537, TA1538, TA98, TA100	Carere and Morpurgo, 1981
Reverse gene mutation	S. typhimurium	99.98	vapor exposure	up to 231.8 μmol/plate	±S-9	positive in TA1535, TA100	Negative in TA98	Barber et al., 1981

TABLE 5-4 (cont.)

Assay	Indicator/ Organism	Compound/ Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse gene mutation	_S. typhimurium_	NR	close plate test	NR	±S-9	positive in TA1535	Exposure system prevented evaporation	Barber and Donish, 1982
Reverse gene mutation	_S. typhimurium_	NR	plate test in dessicator	NR	Aroclor 1254 induced rat and mice liver S-9	positive	Mutagenic response in one or more of TA1535, TA1537, TA100, TA98 with and without metabolic activation	Riccio et al., 1983
Reverse mutation	_S. typhimurium_	NR	plate test	500-15,000 µg/plate	±S-9	positive in TA1535, TA100 with metabolic activation	Negative in TA1537, TA1538, TA98	Moriya et al., 1983
Reverse mutation	_S. typhimurium_	NR	spot test	10 µmol/plate	none	negative	Tester strains TA1538, TA1535, TA100	Buijs et al., 1984
Forward gene mutation	_Streptomyces coelicolor_	analytical grade	spot and plate test	2-100 µℓ/plate	Aroclor 1254 induced rat liver microsomes	negative	Mutation to streptomycin resistance tested	Principe et al., 1981
Forward gene mutation	_S. coelicolor_	NR	spot, plate and liquid tests	2-100 µℓ/plate	Aroclor 1254 induced rat liver microsomes	negative	Streptomycin resistance mutation	Carere and Morpurgo, 1981
Forward gene mutation	_Aspergillus nidulans_	analytical grade	spot and plate test	250, 500 µℓ/ plate	Aroclor 1254 induced rat liver microsomes	negative	Point mutation to 8-azaguanine resistance in strain 35	Principe et al., 1981
Forward gene mutation	_A. nidulans_	NR	spot and liquid test	250, 500 µℓ/ plate	Aroclor 1254 induced rat liver microsomes	negative	8-azaguanine resistance and methionine suppression mutations	Carere and Morpurgo, 1981
Rec assay	_Escherichia coli_	NR	spot test	10 µℓ/disk	none	negative	Wild type DNA polymerase deficient strain tested	Brem et al., 1974; Rosenkranz, 1977

TABLE 5-4 (cont.)

Assay	Indicator/ Organism	Compound/ Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Forward mutation	*E. coli*	NR	plate test	10 mM	Aroclor 1254 induced mouse liver S-9	negative	Strain K12/343/113 tested for mutation to 5-methyltryptophan resistance, galactose utilization and arginine independence	King et al., 1979
Reverse mutation	*E. coli*	analytical grade	plate test	20-10,000 µM	none	very slightly positive	Tryptophan deficient; strain WP2uvrA	Hemminki et al., 1980
Reverse mutation	*E. coli*	NR	plate test	500-15,000 µg/plate	±S-9	negative	WP2hcr tryptophan deficient	Moriya et al., 1983

NR = Not reported

system, with and without glutathione transferases A, B and C. While the activation of 1,2-dichloroethane was NADPH-independent it did not require microsomal mixed-function oxidases since the hepatocyte cytosol fraction elicited increased mutagenesis. Activation required glutathione A or C S-transferase enzymes. Rannug et al. (1978) hypothesized that conjugation of 1,2-dichloroethane to glutathione formed the highly reactive half sulfur mustard, S-(2-chloroethyl)-L-cysteine, which elicited the mutagenic effect. In fact, S-(2-chloroethyl)-L-cysteine gave a strong mutagenic effect at low doses when a metabolic activation was not provided. Since most glutathione conjugates are excreted from the liver in the bile, Rannug and Beije (1979) tested the mutagenicity of bile from 1,2-dichloroethane-treated rats and mice. Consistent with their hypothesis, positive mutagenicity was reported in *S. typhimurium* TA1535 exposed to the bile.

In the bacteria, *Streptomyces coelicolor* and *Escherichia coli*, and the fungi, *Aspergillus nidulans*, generally mutagenicity has not been demonstrated (see Table 5-4). Assays have been conducted for foward gene mutation, reverse mutation and differential growth inhibition (rec assay).

Positive mutagenic responses have been reported for 1,2-dichloroethane in several assays using *Drosophila melanogaster* (Shakarnis, 1969, 1970; Nylander et al., 1978; King et al., 1979) (Table 5-5). In the sex-linked recessive lethal mutation assay, Shakarnis (1969, 1970) exposed two strains of female flies (Canton S and D-32) to 0.07% 1,2-dichloroethane vapor for 4-8 hours. Females were mated with untreated Muller-5 or *In w*^{a}*B* males, and the progeny were scored for sex-linked recessive lethals. For both strains of treated females, the frequency of lethal mutations among progeny was significantly ($p<0.05$) increased in a duration-related manner. Lethal mutations occurred in 0.3% of control Canton S-progeny and 3.22 and 5.91% of

TABLE 5-5

Summary of Mutagenicity Data of 1,2-Dichloroethane on *Drosophila melanogaster**

Assay	Application	Concentration or Dose	Response	Comments	Reference
Sex-linked recessive lethal	air exposure (females)	0.07% vapor for 4, 6 or 8 hours	positive	Duration-related increase in lethal mutations; fertility of treated females reduced	Shakarhis, 1969, 1970
Somatic cell mutations	food exposure (larvae)	0.1, 0.5% in food	positive	Mutations for eye pigment as test parameter; decreased survival of treated	Nylander et al., 1978
Sex-linked recessive lethal	food exposure (male adults)	50 mM	positive	Significant ($p<0.01$) increase in recessive lethal mutations	King et al., 1979

*Compound/purity not reported

progeny exposed for 4 and 8 hours, respectively (Shakarnis, 1969). In progeny from D-32 females, the frequency of lethal mutations was 0.05, 2.0 and 3.3% among controls, 4-hour exposed and 8-hour exposed progeny, respectively.

King et al. (1979) conducted a sex-linked recessive lethal test of 1,2-dichloroethane in _D. melanogaster_ and attempted to identify the sensitive stage of spermatogenesis in exposed males. Berlin K adult male flies were fed for 3 days with 50 mM 1,2-dichloroethane in 5% aqueous sucrose (near LD_{50} level). Treated males were subsequently mated with virgin _Basc_ females at 3-day intervals so that three groups of progeny were produced (9-day mating period). By determining the lethal mutant frequency of the three broods, the particular stage of spermatogenesis that was most sensitive could be identified. The lethal frequency was increased in all broods from treated males compared with controls (0.51, 3.48 and 1.28% for broods I, II and III, compared with 0.21% in controls). Brood II represented progeny sired by flies which were at the spermatid stage during 1,2-dichloroethane treatment.

Nylander et al. (1978) exposed larvae of _D. melanogaster_ to diets containing 0.1 and 0.5% 1,2-dichloroethane and scored the induction of somatic cell sex-linked eye pigment mutations. Larvae were derived from matings of males from a genetically unstable stock (_sc z w_$^{+}$) or a genetically stable stock (_z_ Dp w^{+61e19}) to females with attached X-chromosomes. Mutant male flies had normal, dark red eye pigment. There was a significant increase in mutant eye color flies from both stable and unstable stocks at both dose levels ($p<0.001$). The survival of flies exposed to 1,2-dichloroethane as embryos was significantly reduced (dose-related) compared with controls.

The mutagenicity of 1,2-dichloroethane has been tested im mammalian cell systems in vitro and in mice exposed in vivo (Table 5-6). In cultured CHO cells, a dose-related increase in mutations at the hypoxanthine-guanine phosphorilosyl transferase locus was reported following treatment with 1,2-dichloroethane (Tan and Hsie, 1981; Zamora et al., 1983). Marginal positive responses were reported with and without metabolic activation, but cytotoxic effects when activation was provided prevented testing at doses >3 mM (Tan and Hsie, 1981).

Perocco and Prodi (1981) studied UDS in human lymphocytes exposed to 1,2-dichloroethane in vitro. Peripheral lymphocytes were collected from healthy humans and cultured at 5×10^5 cells/0.2 mℓ for 4 hours with and without 1,2-dichloroethane. Concentrations of 1,2-dichloroethane were 2.5, 5.0 or 10.0 μℓ/mℓ. Tests were performed with and without a PCB-induced rat liver S-9 mix. The authors reported the uptake of ^{3}H-thymidine after 4 hours of culture in treated and control lymphocytes and following pre-treatment with 10 mM hydroxyurea, which suppresses scheduled DNA synthesis. In neither case did the treated lymphocytes show an increase in incorporated ^{3}H-thymidine above control levels when metabolic activation was not present. When metabolic activation was provided, slight but not statistically significant increased ^{3}H-thymidine uptake was indicated. Perocco and Prodi (1981) indicated that 1,2-dichloroethane caused some DNA damage.

In vivo, mice have been used to determine the mutagenic activity of 1,2-dichloroethane in the mouse spot test (Gocke et al., 1983), in the micronucleus test (King et al., 1979; Jenssen and Ramel, 1980), in testicular DNA synthesis inhibition (Borzelleca, 1983) and for hepatocyte DNA damage (Storer and Conolly, 1983; Storer et al., 1984). In the assay for somatic gene mutation, pregnant C57BL mice (mated with T-strain males) were

TABLE 5-6

Summary of Mutagenicity Data on 1,2-Dichloroethane in Mammalian Assay Systems

Assay	Indicator/ Organism	Compound/ Purity (%)	Application	Concentration or Dose	Activating System	Response	Comment	Reference
HGPRT mutation	CHO cells	NR	liquid medium	1.5-50 mM	±S-9 mix	positive	Slight positive response without activation; enhanced mutation response with activation	Tan and Hsie, 1981
HGPRT mutation	CHO cells	NR	collagen gel	8-40 µg/cc vapor	none	positive	Weakly mutagenic; slightly cytotoxic	Zamora et al., 1983
Enhanced viral transformation	Syrian hamster embryo cells	99	media exposure	62-1000 µg/mℓ	none	negative	Viral transformation of Syrian hamster embryo cells by SA7 adenovirus	Hatch et al., 1983
Enhanced viral transformation	Syrian hamster embryo cells	99	vapor exposure	0.04-0.17 mℓ/ℓ	none	positive	Cytolethal at highest level	Hatch et al., 1983
UDS	human lymphocytes *in vitro*	>97	liquid medium	2.5, 5.0, 10.0 µℓ/mℓ	±S-9 mix	slightly positive with S-9	Uptake of H^3-thymidine as measure of UDS	Perocco and Prodi, 1981
Somatic gene mutation	C57BLxT mice	NR	i.p. on the 10th day of gestation	300 mg/kg	NA	equivocal	Hair pigment spots of progeny were determined as regional somatic mutations; significant increase in mutant hair spots compared with untreated controls ($p=0.03$), but not vehicle controls ($p=0.10$)	Gocke et al., 1983
Micronucleus test	NMRI	NR	*in vivo*; i.p.	400 mg/kg x 2 doses	NA	negative	No increase in micronuclei from bone marrow smears	King et al., 1979
Micronucleus test	CBA male mice	NR	*in vivo*; i.p.	100 mg/kg bw	NA	negative	No significant increase in micronucleate erythrocytes after 30 hours of exposure	Jenssen and Ramel, 1980

TABLE 5-6 (cont.)

Assay	Indicator/ Organism	Compound/ Purity (%)	Application	Concentration or Dose	Activating System	Response	Comment	Reference
DNA synthesis in testis	CD-1 mice	NR	in vivo; intra-testicular	100-600 mg/kg	NA	inhibited	Testicular DNA synthesis reduced	Borzelleca and Carchman, 1982; Borzelleca, 1983
Hepatic DNA damage	B6C3F1 male mice	>99.9	in vivo; i.p., oral and inhalation	200-600 mg/kg i.p.; 200-600 mg/kg oral; 150-2000 ppm inhalation x 4 hours	NA	positive (dose-related, all routes)	DNA damage determined by % of double vs. single stranded DNA	Storer and Conolly, 1983; Storer et al., 1984
Dominant lethal	ICR Swiss mice	>99	oral; drinking water	30, 90, 290 mg/ℓ (5, 15, 50 mg/kg/day)	NA	negative	Males used in assay were from multigeneration exposure study and were exposed in utero, during suckling and prior to mating	Lane et al., 1982

NR - Not reported; NA - not applicable

injected intraperitoneally on day 10 of gestation with 300 mg 1,2-dichloroethane/kg. The appearance of mutant spots of hair on progeny was the indicator of mutagenic potency (Gocke et al., 1983). The incidence of mutant hair spots was increased in treated mice compared with untreated controls ($p=0.03$), but not compared with vehicle controls ($p=0.18$). The findings were therefore inconclusive (see Table 5-6).

In both micronucleus tests in mice (King et al., 1979; Jenssen and Ramel, 1980), intraperitoneal treatment with 1,2-dichloroethane caused no significant increase in micronuclei in polychromatic erythrocytes (see Table 5-6). Borzelleca (1983) indicated that intratesticular injection of 1,2-dichloroethane at 100-600 mg/kg bw caused inhibited testicular DNA synthesis in CD-1 mice.

The effects of _in_ _vivo_ exposure to 1,2-dichloroethane on hepatocyte DNA was examined by Storer and Conolly (1983) and Storer et al. (1984). Male B6C3F1 mice were treated with 1,2-dichloroethane by intraperitoneal injection (200-600 mg/kg bw), orally by gavage (200-600 mg/kg bw) and by inhalation (4-hour exposure at 150-2000 ppm). Hepatocyte DNA damage was estimated using an alkaline DNA unwinding assay to determine the presence of single stranded breaks. Hepatocyte DNA damage was increased in a dose-related manner in animals treated by all routes of exposure (Storer et al., 1984).

Lane et al. (1982) conducted multigeneration exposure studies of 1,2-dichloroethane and selected second the third generation males for dominant lethal testing. Males used in the study were exposed _in_ _utero_, during suckling and thereafter until mating at ~9 weeks of age. Exposure was via drinking water at levels of 0, 30, 90 and 290 mg/ℓ, providing nominal dosages of 0, 5, 15 and 50 mg/kg/day for a 35 g mouse (assuming 6 mℓ/day water consumption). Additional details of the protocol are reviewed in Section 5.3. Treated males were mated with untreated females. Fetal implants, resorptions and deaths were determined at ~14 days of gestation. The results of this study show no evidence of increased fetal mortality and, therefore, no indication of dominant lethal mutations (see Table 5-6).

The mutagenicity of 1,2-dichloroethane is regarded by several researchers conducting mutagenicity tests to be due to an active protein-binding metabolite of the parent compound. Banerjee and Van Duuren (1979) reported that 1,2-dichloroethane bound covalently with hepatic microsomal proteins and to salmon sperm DNA. The authors also noted a 6- to 8-fold increase in the binding of 1,2-dichloroethane to hepatic microsomal protein from B6C3F1 mice compared to Osborne-Mendel rats. Binding to sperm DNA was 5 times greater in the presence of microsomal preparations from B6C3F1 mice than Osborne-Mendel rats. The authors felt that a metabolite of 1,2-dichloroethane was the active binding compound, since inhibitors of microsomal oxidation blocked binding. Hemminki et al. (1980) indicated that 1,2-dichloroethane, tested without metabolic activation, had no alkylating activity on 4-(p-nitrobenzyl) pyridine or deoxyguanosine. Van Bladeren et al. (1981) studied the role of glutathione conjugation, mediated by glutathione transferase. on the mutagenic activity of 1,2-dichloroethane. These studies found S-(2-chloroethyl) glutathione to be the conjugation product of 1,2-dichloroethane, and found the metabolite to be a much stronger mutagen than the parent compound. S-(2-chloroethyl) glutathione was regarded as the reactive, mutagenic agent. After examination of amino acid adducts from proteins covalently bound by 1,2-dichloroethane, Maiorino et al. (1982) reported that several adducts were identified. This indicated that 1,2-dichloroethane, or its metabolite (since metabolic activation was provided), bound nonselectively at several sites. Rinkus et al. (1983) demonstrated the formation of adenine adducts (etheno-adenosine) following microsomal metabolism of 1,2-dichloroethane.

5.2.2. 1,1-Dichloroethane. Riccio et al. (1983) assessed the mutagenicity of 1,1-dichloroethane using S. typhimurium tester strains TA1535, TA1537, TA98 and TA100. Metabolic activation, the S-9 liver fraction from Aroclor 1254-induced rats and mice, was present and absent in plate cultures that were incubated in desiccators for 8 hours. 1,1-Dichloroethane reportedly caused an increase in revertant colonies in one or more tester strain both with and without metabolic activation, but the affected strain(s) was not specified. There was apparently no appreciable difference in mutagenic response with or without metabolic activation.

Using the enhancement of viral transformation of Syrian hamster embryo cells as a measure of chemical damage to mammalian cell DNA, Hatch et al. (1983) reported that 1,1-dichloroethane produced a positive response. Syrian hamster embryo cells were cultured and exposed to 1,1-dichloroethane in closed chambers for ~20 hours prior to virus inoculation. Adenovirus SA7 was inoculated for 3 hours prior to washing and replating of cells for survival and transformation determinations. The number of transformed colonies from chemical-treated and viral-inoculated cells was compared with the number of transformed colonies from virus-inoculated controls. 1,1-Dichloroethane at 0.062-0.50 mℓ/4.6 ℓ chamber showed a significant ($p<0.05$) enhancement of virally affected cells compared with virus-inoculated controls. At 1.0 mℓ/4.6 ℓ chamber, 1,1-dichloroethane was toxic to cells and no colonies survived treatment.

5.3. TERATOGENICITY

A teratogenicity study of 1,2-dichloroethane was conducted by the Dow Chemical Company using Sprague Dawley rats and New Zealand White rabbits (Schlacter et al., 1979). Groups of 16-30 pregnant rats were exposed by inhalation to 0, 100 or 300 ppm (0, 405 or 1214 mg/m^3) 1,2-dichloroethane for 7 hours/day on days 6-15 of gestation. Pregnant rabbits, 19-21/group, were exposed at the same concentrations and exposure schedule on days 6-18 of gestation. The animals were sacrificed on day 21 or 29 of gestation for rats and rabbits, respectively, and uteri were examined for resorption sites and live and dead fetuses. Fetuses were weighed, measured for length and examined for external abnormalities, soft tissue alterations (one-third of animals/group examined) and skeletal abnormalities.

Specific data relevant to the teratogenicity of 1,2-dichloroethane in rats were limited, because no major malformations were detected among fetuses of dams exposed at 100 ppm, and no fetuses survived from the 300 ppm dose group. The incidence of a minor skeletal variation, bilobed thoracic centra, was decreased among litters of rats exposed in utero at 100 ppm 1,2-dichloroethane (1 litter affected vs. 7 control litters). Maternal toxicity in rats exposed at 300 ppm was severe, with 10 deaths among 16 treated rats. Only one dam of the six survivors had implantation sites, all of which were resorbed.

In rabbits, maternal toxicity and mortality also occurred, with 0/20, 4/21 and 3/19 deaths among control, low dose and high dose groups, respectively. Exposure did not, however, appear to affect pregnancy, litter size, fetal measurements or resorption incidence. The incidence of major malformations was not increased among litters of treated rabbits (high or low dose group) compared with controls. A decrease in minor skeletal alterations (lumbar spurs, extra ribs) was reported among treated litters, but the decreases were not regarded as treatment-related.

A multigeneration reproduction study conducted by Lane et al. (1982) examined the teratogenic effects of 1,2-dichloroethane administered in drinking water to male and female ICR Swiss mice. 1,2-Dichloroethane was administered at 0, 0.03, 0.09 or 0.29 mg/mℓ (0, 30, 90, 290 mg/ℓ), giving nominal daily doses of 5.0, 15 or 50 mg/kg/day (assuming water consumption at 6 mℓ/day for a 35 g mouse). Test animals were maintained on the treated drinking water throughout the study. The parental mice (10 males and 30 females) were mated at 5 weeks after treatment was started (producing F_{1a} progeny), 2 weeks after weaning of the F_{1a} litters (producing F_{1b} progeny) and 2 weeks after weaning of the F_{1b} litters (producing the F_{1c}). The F_{1a} litters were used for 21-day survival tests. Randomly selected F_{1b} mice were used as second-generation parents and were continued on treatment for 11 weeks prior to mating to produce F_2 progeny. The F_{1c} females were used in teratogenicity studies; therefore, treatment was continued from birth until they were mated (~9 weeks of age) with untreated males. The F_{1b} adults were mated twice, producing F_{2a} and F_{2b} litters. The F_{2a} litters were used in 21-day survival tests, while the F_{2b} females were used for a teratology study. Males of the F_{1c} and F_{2b} litters were used in dominant lethal studies (reviewed in Section 5.2.). Data from the multigeneration exposure studies indicate that at the dose levels tested, no significant increase in gross, visceral or skeletal anomalies occurred and embryo/fetotoxic effects were not produced. Due to the low doses, which produced no signs of toxicity, it is not possible to determine conclusively the potential of 1,2-dichloroethane to cause teratogenic or embryotoxic effects.

The teratogenic potential of 1,1-dichloroethane was tested by Schwetz et al. (1974) using Sprague Dawley rats exposed by inhalation. Groups of 16 and 18 pregnant rats were exposed at respective concentrations of 3800 and 6000 ppm (15,380 and 24,285 mg/m³) for 7 hours/day on days 6-15 of gestation. Maternal weight gain and food consumption were decreased and liver weight was increased among rats exposed at both levels compared with controls. No effect on conception rate, implantations or litter size was evident. Fetal body weight and length were comparable between treated and control groups, but the increased incidence of delayed ossification of sternebrae among fetuses of the high dose group suggests fetotoxicity. The incidence of split vertebral centra was significantly lower in fetuses of rats exposed at 3800 ppm 1,1-dichloroethane, but not in high dose fetuses. No other gross, soft-tissue or skeletal anomalies had a significantly different incidence in fetuses of treated dams compared with controls (Schwetz et al., 1974).

In a Russian study (available only as an abstract), Gostinskii (1966) reported that 1,1-dichloroethane was given by inhalation to pregnant rats on day 10 of gestation at various concentrations for 6 hours. At 7.8 mg/ℓ (7800 mg/m^3), 1,1-dichloroethane was lethal to all dams, while 6.5 mg/ℓ (6500 mg/m^3) was lethal to fetuses. Surviving fetuses exposed at 1.3-5.2 mg/ℓ (1300-5200 mg/m^3) were examined for gross abnormalities, but none were found.

5.4. OTHER REPRODUCTIVE EFFECTS

As reviewed by Barlow and Sullivan (1982), data regarding the possible effects of occupational exposure to 1,2-dichloroethane on the reproductive physiology in women has been reported in a Russian study (Mukhametova and Vozovaya, 1972) of female glue workers. Women were exposed primarily to benzene, 1,2-dichloroethane and methylene chloride used as glue solvents. The average level of both chlorinated hydrocarbons combined in breast milk of glue workers was 0.074 mg/kg, which persisted 17 hours after exposure had ceased. An increase in the incidence of menstrual and gynecological disorders was reported in the female glue workers. Infertility rates of the exposed women were not different from that in control groups (Mukhametova and Vozovaya, 1972). An increase in the incidence of "toxicoses," spontaneous abortions and complications during labor were also observed among the female glue workers. Data from this study provide only suggestive evidence that 1,2-dichloroethane effects reproductive physiological processes in women. 1,2-Dichloroethane may have contributed to the reported effects, but the mixed exposure (exposure levels of components not specified) precludes any conclusion.

The effects of 1,2-dichloroethane on reproduction in rats were studied by Lane et al. (1982), Rao et al. (1980), Murray et al. (1980) and Alumot et al. (1976). In the multigeneration study by Lane et al. (1982), 1,2-dichloroethane was given in the drinking water continuously, before, during and after the mating, gestation and neonatal development for two generations (F_1 and F_2 generations). (Details of the protocol of the 3-generation study are given in Section 5.3.) Based on the number of pregnant females, implants/litter, resorptions, live fetuses and 21-day neonatal survival determined in three treatment groups (30, 90, 290 mg/ℓ) in F_1 and F_2 generations, a dose-related decrease in fertility index or reproductive capacity was not evident. The number of dead fetuses/live fetuses was elevated in vehicle controls (1% emulphor) of both generations so that frequency of death among treatment groups was often lower than vehicle controls but comparable to untreated controls. Neonatal survival to days 4 and 21 were not different between treated and control groups.

Alumot et al. (1976) conducted reproduction tests of 1,2-dichloroethane administered to rats in fumigated mash diet at levels of 250 and 500 ppm. Groups of 18 rats of each sex (strain not specified) were exposed to the treated diet for 6 weeks prior to mating and during all intervals between mating periods. Initial matings were between treated females of each dose group and untreated males. Subsequent matings (up to seven matings were conducted during the 2-year study) were performed using 72 females (apparently parentals and F_1 females) and 45 treated males from the same dose groups. Matings were conducted at ~2-month intervals, allowing 10 days of cohabitation of one male with two females. During the 10-day mating period, the control diet was given to all rats. Parameters used to estimate reproductive performance were percent of pregnant/mated dams, percent of litters/pregnancies, mean litter size, mortality of progeny and body weight of young (at birth and weaning). Results of these studies indicated that pup mortality and weight were not affected by in utero and lactational exposure to 1,2-dichloroethane. Fertility and reproductive activity of male and female rats ingesting 1,2-dichloroethane were not different from controls. Fertility in females decreased as dams aged, but this was seen in both control and treated rats.

The reproduction study reported by Rao et al. (1980) and Murray et al. (1980) was conducted using groups of 20 Sprague-Dawley rats of each sex exposed by inhalation at 25, 75 or 150 ppm (101, 304 or 607 mg/m³) 1,2-dichloroethane (6 hours/day, 5 days/week) for 60 days. The control group, maintained in exposure chambers, consisted of 30 animals of each sex. Rats were mated after the 60-day exposure period, one-to-one within the treatment groups, to produce the F_{1a} generation. Exposure was continued during gestation (6 hours/day, 7 days/week), discontinued from day 21 of gestation to 4 days postpartum and resumed until the second breeding cycle. Seven days after the F_{1a} litters were sacrificed (at age 21 days), the parental rats were remated to produce the F_{1b} generation. Male rats were exposed continuously from the start of the experiment, initially on 5 days/week (for

60 days), then on 7 days/week (Rao et al., 1980). No maternotoxic effects of inhaled 1,2-dichloroethane occurred in any treatment group. Data regarding fertility and reproduction from the F_{1a} and F_{1b} litters showed no dose-related effects. Fetal mortality and neonatal survival (at 1, 7, 14 and 21 days) were comparable between all treatment groups and controls. Exposures did not affect neonatal body weight or growth to weaning in F_{1a} or F_{1b} generations.

Vozovaya (1974) reported effects on reproductive capacity among female rats exposed to 1,2-dichloroethane by inhalation. A group of 28 female rats (strain not specified) was exposed at 14±2.5 ppm (57±10 mg/m³) for 4 hours/day on 6 days/week for 6 months prior to mating, and during pregnancy and rearing of young. During the pre-mating exposure period, the average length of the estrus cycle was increased but females did not become infertile. Matings were conducted with untreated males after the 6-month exposure period. Treated females took more days with males (pair-days) before becoming pregnant, compared with controls. The average litter size of treated dams was significantly ($p<0.05$) reduced ($n=6.5\pm1.1$) compared with controls ($n=9.7\pm0.6$), but it could not be determined if reduced litter sizes were due to reproductive effects in females or increased embryo and/or fetal death. The increased incidence of stillbirths, 23.1% in treated dams vs. 5.1% in controls, suggests a fetotoxic effect. Birth weight of treated pups was also reduced (5.1 g) compared with controls (6.4 g). Mortality during the first month after birth (exposure was continued) was 20% in treated pups and only 3% in controls. The post-weaning growth rate of treated female offspring was decreased compared with controls, while males were unaffected. Maturation and development of offspring exposed in utero were otherwise normal. Prolonged estrus was also noted in female offspring inhaling 1,2-dichloroethane. At 3 months of age, the female offspring exposed in utero and continuously after birth were mated with untreated males. Fertility of the F_1 females was not affected, but neonatal mortality was 18% in treated litters compared with 7% in controls. These data (Vozovaya, 1974) suggest an effect on fetal and neonatal survival following in utero and inhalation exposure to 1,2-dichloroethane at levels of 14 ppm; however, the reliability of these findings is questionable in view of the negative results of Rao et al. (1980) at much higher exposure levels.

The effects of exposure to 1,1-dichloroethane by inhalation on the reproductive capacity of pregnant female Sprague-Dawley rats was studied by Schwetz et al. (1974). Groups of 20 females were exposed at 3800 or 6000 ppm (16,380 or 24,385 mg/m^3) 1,1-dichloroethane for 7 hours/day on days 6-15 of gestation. Treatment caused maternal toxicity, but there were no significant dose-related effects on the number of implants, live fetuses or resorptions/dam. Fetal body weight and length were not different from controls in either dose group (Schwetz et al., 1974).

5.5. CHRONIC TOXICITY

Available data regarding the effects of chronic exposure to 1,2-dichloroethane in humans are limited and are found primarily in the foreign literature. Two Russian studies (Kozik, 1957; Rozenbaum, 1947) and two Polish studies (Cetnarowicz, 1959; Brzozowski et al., 1954) of the health effects of long-term occupational exposure to 1,2-dichloroethane were reviewed by the U.S. EPA (1984a). Other studies that poorly document exposure levels and toxic effects were reviewed by the U.S. EPA (1983a). Workers were usually exposed to 1,2-dichloroethane during its use as a solvent (in glues or oil extraction process) or soil fumigant. Exposure levels in air ranged from 4-200 ppm (16-809 mg/m³) in the different usage areas but were generally <50 ppm (<202 mg/m³). NIOSH (1976) suggests that most repeated occupational exposures are at 10-100 ppm (40-405 mg/m³) 1,2-dichloroethane. The morbidity survey by Kozik (1957) on workers exposed to 1,2-dichloroethane as a glue solvent showed high occurrence rates for gastrointestinal, liver, bile duct and gall bladder diseases (19/83), goiter and hyperthyroidism, neurotic conditions, autonomic dystonia and asthenic conditions among 83 workers compared with factory controls. Exposure levels ranged from 11-28 ppm (45-113 mg/m³) but averaged 10-15 ppm (40-61 mg/m³) (NIOSH, 1976).

In a report of health effects in mineral oil purification workers where 1,2-dichloroethane [levels up to 200 ppm (809 mg/m³)] was used as a solvent, Cetnarowicz (1959) identified liver effects and gastrointestinal tract irritation as probably related to exposure to this solvent. A study by Rozenbaum (1947) of 100 workers from several industries associated functional nervous system disorders with exposure to 1,2-dichloroethene. In agricultural workers (n=118) using 1,2-dichloroethane as a soil fumigant [exposure levels near 4 ppm (16 mg/m³)], medical findings associated with exposure included conjunctival congestion, respiratory irritation, weakness, headache, liver pain and tachycardia. Fatigue, headache, irritation of the eyes and respiratory tract, liver and kidney dysfunction, epigastric pain and nausea have been associated with repeated and acute exposure to 1,2-dichloroethane (U.S. EPA, 1984a; IARC, 1979; Drury and Hammons, 1979).

The carcinogenicity bioassay of 1,2-dichloroethane conducted by the NCI (1978a) in Osborne-Mendel rats and B6C3F1 mice is useful in determining chronic toxic effects of the compound following gavage treatment. Groups of 50 animals of each sex and species were treated at two dose levels (47 and

95 mg/kg/day in rats; 97 and 195 mg/kg/day in male mice; 149 and 299 mg/kg/day in female mice) for 78 weeks and allowed 15-32 (rats) or 12-13 (mice) weeks observation after treatment. Additional details of this study are presented in Section 5.1. In rats, the major toxic effect was a significant ($p<0.001$) increase in mortality in high dose males and females. Mortality reached 50% by 55 (males) and 57 weeks (females) in high dose rats, compared with 75-90 weeks in low dose and vehicle controls. High mortality also occurred in high dose female mice ($p<0.001$) compared with low dose and control groups, but deaths may have been tumor-related since 25/36 mice that died between weeks 60 and 80 had tumors. Mortality in male mice was comparable among all groups.

The toxic effects of 1,2-dichloroethane administered to rats in fumigated mash feed for 2 years were studied by Alumot et al. (1976). Groups of 18 rats (strain not specified) of each sex were given diets containing 1,2-dichloroethane at 0, 250 or 500 ppm for 24 months. During the exposure period, rats were bred up to 7 times as part of the reproduction study (see Section 5.4.). Growth, food consumption and mortality between the different dose groups and controls were comparable. Chronic respiratory disease was the cause of most deaths, with males being more susceptible than females, but treatment did not increase mortality. Treatment at the levels tested had no apparent effects on reproductive capacity (see Section 5.4.). Biochemical examination of blood and post-mortem examination revealed no toxic effects associated with chronic 1,2-dichloroethane ingestion at the dietary levels tested (Alumot et al., 1976).

Munson et al. (1982) conducted a 90-day drinking water study and a 14-day gavage study of 1,2-dichloroethane to determine its effects on the immune response of male CD-1 mice. The TWA doses were 3, 24 and 189 mg/kg/day for 90 days or 4.9 and 49 mg/kg/day for 14 days. Groups of 32 mice were exposed at each dose level. Hematological parameters (hematocrit, hemoglobin, erythrocyte and platelet counts), coagulation indices and serum chemistry parameters were not affected during 90-day exposures to 1,2-dichloroethane. The number of splenic AFC (stimulated by sheep erythrocytes) was slightly increased in mice exposed at 189 mg/kg/day for 90 days but not significantly so. A significant ($p<0.05$) reduction in AFC was noted at both dose levels after 14 days of exposure. A dose-related reduction of hemagglutination was indicated in the 90-day study, but the reduced response was not significantly affected. Cell-mediated immunity (delayed hypersensitivity to sheep erythrocytes and T-lymphocyte response to concanavalin A) was not affected by exposure to 1,2-dichloroethane at the levels tested for 90 days, but 14-day exposures produced slightly significant ($p<0.05$), nondose-related reduced responses at both dose levels. This study suggested that effects of the immune system occurred after 14 days of gavage treatment but not after 90-day drinking water exposure, even at a higher dose level. Metabolism of 1,2-dichloroethane during the drinking water exposure may have effectively reduced the amount of compound reaching the effector site, while bolus gavage doses allowed less metabolism (Munson et al., 1982).

Borzelleca (1983) reported that kidneys were affected in male and female CD-1 mice exposed to 4, 24-25 and 186-188 mg 1,2-dichloroethane/kg/day in the drinking water for 90 days. A complete battery of parameters, including hematology, clinical chemistry, immunology, behavior, reproduction, neurochemical and organ weights, were studied to determine toxic effects. This study was conducted under contract for the U.S. EPA and additional details regarding the apparent toxic effects were not available.

In a long-term inhalation bioassay of 1,2-dichloroethane, Spreafico et al. (1980) exposed Sprague-Dawley rats at 250 to 150, 50, 10 and 5 ppm (1012 to 607, 202, 40 and 20 mg/m³) for 7 hours/day, 5 days/week for up to 18 months. Interim kills were made at 3, 6 and 12 months prior to the terminal sacrifice at 18 months. Rats sacrificed at 3, 6 and 18 months were started on the treatment at age 3 months, while rats aged 14 months were used for the 12-month measurements. In rats exposed from 3 months of age to levels up to 150 ppm, no significant toxic effects were evident. Hematological, clinical chemistry, serum enzymes and urinalyses were performed, and the only apparent treatment-related effect was an increased level of serum lactate dehydrogenase among treated male rats (no clear dose-related response). Exposure of the aged rats to 1,2-dichloroethane for 12 months resulted in altered serum chemistry profiles, suggesting changes in liver and kidney function. SGPT, γ-glutamine transpeptidase (females only), blood glucose and uric acid levels were increased in rats exposed at 50 and 150 ppm. SGOT and cholesterol levels were depressed after exposure at 50 and 150 ppm (Spreafico et al., 1980). No histological examinations to confirm these suspected liver and kidney toxicities were reported in the study.

Maltoni et al. (1980) exposed Sprague-Dawley rats and Swiss mice by inhalation to 250 to 150, 50, 10 and 5 ppm (1012 to 607, 202, 40 and 20 mg/m³) 1,2-dichloroethane for 7 hours/day, 5 days/week for up to 78 weeks during a carcinogenesis bioassay (see Section 5.1.). The only toxic effect reported was a high level of mortality among female rats and mice exposed at 250 ppm during the early weeks of the study. This caused the researchers to lower the exposure level to 150 ppm for the remainder of the study (Maltoni et al., 1980).

Several early inhalation studies of 1,2-dichloroethane (Heppel et al., 1946; Spencer et al., 1951; Lioia et al., 1959a,b; Hofmann et al., 1971) reported increased mortality and altered hepatic and renal function with histological changes in several species exposed for periods of 6 weeks to 8 months. Heppel et al. (1946) exposed rats, guinea pigs, rabbits, cats, dogs, pigs and monkeys to 1,2-dichloroethane at 100, 200, 400 and 1000 ppm (405, 809, 1619 and 4047 mg/m^3) for 7 hours/day, 5 days/week for up to 8 months. At 1000 ppm most animals died within 8 weeks of treatment; guinea pigs and rats appeared to be the most sensitive species. Common pathological changes included renal tubule degeneration, congestion and fatty changes of the liver, splenitis and pulmonary congestion. Exposure at 400 ppm resulted in high levels of mortality in rats, guinea pigs and rabbits. All dogs (n=9) treated at this level survived for 167-177 exposures, but five exhibited slight fatty changes of the liver. At a concentration of 200 ppm 1,2-dichloroethane, mortality was increased in rats, mice and guinea pigs, with male Osborne-Mendel rats and mice being most sensitive. Mortality was 8/12 after 6 exposures in male Osborne-Mendel rats, 7/12 after 73 exposures in Wistar rats, 18/20 after 7 exposures in mice and 5/14 after 115 exposures in guinea pigs (Heppel et al., 1946). Exposure at 100 ppm 1,2-dichloroethane (7 hours/day, 5 days/week) for 4 months produced no observable clinical or histopathological effects among 39 rats, 16 guinea pigs and 19 juvenile mice.

Spencer et al. (1951) exposed groups of rats (15 of each sex), guinea pigs (8 of each sex), rabbits (2 male, 1 female) and monkeys (2 male) to 400 and 100 ppm (1619 and 405 mg/m^3) 1,2-dichloroethane for 7 hours/day, 5 days/week for up to 36 weeks. Groups of rats and guinea pigs were also exposed to 200 ppm (809 mg/m^3) on the same dosing regime. At 400 ppm, all female rats died within 10 exposures and all males died within 40 days of exposure. Mortality reached 100% in male and female guinea pigs treated at 400 ppm within 10 and 24 exposures, respectively, and both monkeys died, one after 8 and the other after 12 exposures at 400 ppm. Rabbits showed no toxic effects after 165 exposures at 400 ppm. Toxic effects produced in rats, guinea pigs and monkeys included enlarged liver and kidneys, cloudy swelling of the liver, and renal tubular swelling and degeneration. In rats exposed at 200 ppm for 151 exposures, no adverse effects on behavior, growth or gross and microscopic histology of organs were noted. Exposure to 200 ppm 1,2-dichloroethane for 180 exposures resulted in decreased body weight and increased liver weight in male guinea pigs, and slight hepatic degeneration in half of the guinea pigs of both sexes. No adverse effects were seen in any of the four species exposed to 1,2-dichloroethane at 100 ppm for 121-178 exposures (Spencer et al., 1951).

Lioia and Elmino (1959), Lioia and Fondacaro (1959) and Lioia et al. (1959a,b) exposed 10 rabbits to 3000 ppm (12,142 mg/m^3) 1,2-dichloroethane by inhalation for 2 hours/day, 5 days/week for 90 days. Anemia with leukopenia and thrombocytopenia were reported among treated rabbits. Bone marrow histology revealed granuloblastic and erythroblastic hyperplasia. Liver function was slightly altered, with a decreased albumin-to-globulin ratio, slightly elevated BSP retention and slightly elevated cephalin-cholesterol flocculation test values. Kidney function was also affected, with altered creatinine clearance, portal blood flow and glomerular filtration rate. Histologically, congestion, vascular degeneration and focal necrotic areas were observed in the liver and kidneys.

Hofmann et al. (1971) conducted subchronic toxicity studies of 1,2-dichloroethane administered by inhalation to groups of 10 rats, 10 guinea pigs, 4 rabbits and 4 cats. Exposure was to 100 or 500 ppm (405 or 2024 mg/m³), 6 hours/day, 5 days/week for 6 weeks. Mortality was high in all species following exposure at 500 ppm. Toxic effects observed at autopsy were reported in the liver, kidneys, adrenals, heart and lungs. At 100 ppm, exposed cats showed poor growth compared with controls. No other toxic effects were observed in animals exposed at 100 ppm 1,2-dichloroethane.

The NCI (1978b) carcinogenesis bioassay could be used to elucidate chronic toxic effects of 1,1-dichloroethane on Osborne-Mendel rats and B6C3F1 mice. The study protocol and dosing regimen have been reviewed in Section 5.1. High mortality rates due to pneumonia among treated and control rats and mice preclude the conclusive demonstration of chronic toxic effects in rats and mice gavaged at either dose level. The incidence of non-neoplastic lesions among treated rats and mice was similar to that in control groups.

Hofmann et al. (1971) exposed groups of rats, guinea pigs, rabbits and cats to 1,1-dichloroethane at 500 ppm (2024 mg/m³) for 6 hours/day, 5 days/week for 13 weeks. Because no adverse signs of toxicity were observed after this exposure interval, animals were exposed for an additional 13 weeks at 1000 ppm (4047 mg/m³). Rats, guinea pigs and rabbits tolerated the additional exposure as well, with no apparent toxic effects. In cats, renal injury with histological change and increased blood urea developed after the additional 13-week exposure at 1000 ppm 1,1-dichloroethane.

In an unpublished Dow Chemical Company (n.d.) study, rats, guinea pigs, rabbits and dogs were exposed by inhalation to 1,1-dichloroethane at 500 or 1000 ppm (2024 or 4047 mg/m³) for 7 hours/day, 5 days/week for 6 months. After hematological studies and gross and microscopic pathological examinations, no toxic effects attributable to exposure were observed in any species.

5.6. OTHER RELEVANT INFORMATION

The effects of acute exposure, primarily by inhalation, in humans have been established based on case reports of occupational exposure (U.S. EPA, 1984a). Both fatal and non-fatal cases usually have poorly documented exposure levels and deal with complex exposures. Signs and symptoms of acute exposure to 1,2-dichloroethane include gastrointestinal discomfort, CNS disturbances, respiratory irritation and clinical evidence of renal and hepatic dysfunction. Deaths usually are ascribed to respiratory and circulatory failure with pulmonary edema and congestion and degeneration, hemorrhage and necrosis of most major organs (U.S. EPA, 1984a).

In animals, acute inhalation exposure elicits effects similar to those reported in humans. Narcosis, a sign of CNS depression, occurs initially following high level exposure, with histopathological changes developing subsequently. Affected organs include the liver, kidneys, spleen, lungs and adrenals. In rats single 5- to 8-hour exposures at 200 ppm (809 mg/m^3) caused no apparent toxic effects (Spencer et al., 1951). Toxic effects usually occur at ~300 ppm (1214 mg/m^3) for 5- to 8-hour exposures, with levels >600 ppm (2428 mg/m^3) causing death (Spencer et al., 1951; Heppel et al., 1945). The U.S. EPA (1984a) review presents additional acute toxicity data on 1,2-dichloroethane. The oral LD_{50} is ~0.7 g/kg for rats and ~0.45 g/kg for mice (U.S. EPA, 1984a.)

Acute toxicity data regarding 1,1-dichloroethane are limited. Browning (1965) reported that 1,1-dichloroethane was discontinued as a human anesthetic because of its cardiac-stimulating effects. In rats, an 8-hour exposure at 4000 ppm (16,190 mg/m^3) 1,1-dichloroethane caused no mortality, while 16,000 ppm (64,759 mg/m^3) was lethal (Smyth, 1956).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

Acute toxicity tests in aquatic species have primarily determined lethal levels of 1,2-dichloroethane in freshwater and marine species, but some data regarding the 1,1-isomer are available. Johnson and Finley (1980) reported a 96-hour LC_{50} value of 225 mg 1,2-dichloroethane/ℓ for the rainbow trout, Salmo gairdneri. The U.S. EPA (1978) conducted a battery of toxicity tests of 1,2-dichloroethane including acute tests in the bluegill sunfish, Lepomis macrochirus. The 24-, 48-, 72- and 96-hour LC_{50} values were >600, >600, 592 and 431 mg/ℓ, with a NOEC of <78 mg/ℓ (U.S. EPA, 1978; Buccafusco et al., 1981). Walbridge et al. (1983) reported that the 24-, 48-, 72- and 96-hour LC_{50} values for fathead minnows, Pimephales promelas, were 141, 118, 116 and 116 mg 1,2-dichloroethane/ℓ, respectively. In the same species (P. promelas), Veith et al. (1983) reported a 96-hour LC_{50} of 118 mg 1,2-dichloroethane/ℓ. In the guppy, Poecilia reticulata, LC_{50} values following 7 days of exposure were 106 mg 1,2-dichloroethane/ℓ and 202 mg 1,1-dichloroethane/ℓ (Konemann, 1981; Koch, 1982). Knie et al. (1983) reported EC_0, EC_{50} and EC_{100} values (duration not reported) of 1.3, 1.8 and 2.4 mg 1,2-dichloroethane/ℓ in the golden orfe, Leuciscus idus. Applegate et al. (1957) reported no effects on rainbow trout, S. gairdneri, or larval lampreys, Petromyzon marinus, exposed to 5 mg 1,2-dichloroethane/ℓ for 24 hours.

In the marine sheepshead minnow, Cyprinodon variegatus, LC_{50} values determined for 24-96 hours were between 126 and 226 mg 1,2-dichloroethane/ℓ, with no effects at 126 mg/ℓ (U.S. EPA, 1978; Heitmuller et al., 1981; Koch, 1982). In the marine dab (species not specified), a 96-hour LC_{50} value of 115 mg/ℓ was determined for 1,2-dichloroethane

(Pearson and McConnell, 1975). In marine acclimated pinperch, Lagodon rhomboides, Garrett (1957) reported LC_{50} values of 150-175 mg 1,2-dichloroethane/ℓ and 250-275 mg 1,1-dichloroethane/ℓ.

Toxicity tests using the freshwater crustacean, Daphnia magna, have resulted in 24- and 48-hour LC_{50} values of 246 and 218 mg 1,2-dichloroethane/ℓ and a NOEC of <68 mg/ℓ (U.S. EPA, 1978; LeBlanc, 1980). Bringmann and Kuehn (1982) reported 24-hour LC_0, LC_{50} and LC_{100} values of 385, 540 and 682 mg/ℓ for 1,2-dichloroethane in D. magna. Using fed and unfed Daphnia, Richter et al. (1983) reported 48-hour LC_{50} values of 320 and 270 mg 1,2-dichloroethane/ℓ and 48-hour EC_{50} values for immobilization of 180 and 160 mg/ℓ, respectively. Knie et al. (1983) reported EC_0, EC_{50} and EC_{100} values at 67, 600 and 6700 mg 1,2-dichloroethane/ℓ in D. magna (duration not specified). Johnson and Finley (1980) reported that the 96-hour LC_{50} values for the scud, Gammarus fasciatus, and the stonefly larvae, Pteronarcys californica, were >100 mg 1,2-dichloroethane/ℓ.

Toxicity tests in the marine shrimp, Artemia salina, were conducted using 1,2-dichloroethane at concentrations from 100-1000 mg/ℓ (Price et al., 1974). The 24-hour LC_{50} was determined to be 320 mg/ℓ. In the mysid shrimp, Mysidopsis bahia, 24-, 78-, 72- and 96-hour LC_{50} values were 108, 110, 112 and 113 mg 1,2-dichloroethane/ℓ (U.S. EPA, 1978). Evaporative loss may have contributed to the same toxicity level at various time periods. The NOEC was 75.4 mg/ℓ in this marine shrimp. In the shrimp, Crangon crangon, 100% mortality was reported within 7 hours during exposure to 300 mg 1,2-dichloroethane/ℓ. The 24-hour LC_{50} value was ~170 mg/ℓ, and the 48-hour value was expected to be near this level (Rosenberg et al., 1975). The 48-hour LC_{50} of 1,2-dichloroethane to barnacle nauplii, Elminius modestus, was 186 mg/ℓ (Pearson and McConnell, 1975).

6.2. CHRONIC EFFECTS

Embryo-larval stages of fish (S. gairdneri) and amphibians (Rana pipiens and Ambystoma gracile) were used in toxicity tests of 1,2-dichloroethane conducted by Black et al. (1982). Exposure was started within 30 minutes of fertilization and continued throughout embryo development until hatching (23, 5.5 and 5 days) and 4 days post-hatching. The number of abnormal embryos, survival at hatching and survival at 4 days post-hatching were determined. In the rainbow trout, survival at hatching and 4 days post-hatching were the same: 98, 96, 89, 82, 70 and 52% of controls after exposure to 0.002, 0.026, 0.20, 1.57, 3.49 and 34.4 mg 1,2-dichloroethane/ℓ, respectively. In the leopard frog, R. pipiens, a few deaths occurred from hatching until 4 days post-hatching, but survival was nearly identical at both times. Survival at 4 days post-hatching was 96, 91, 86, 74, 54 and 24% of controls in embryo-larval frogs exposed to 0.002, 0.009, 0.19, 1.07, 2.69 and 21.9 mg/ℓ. No teratogenic effects were observed at the three lowest dose levels, while 3, 6 and 25% of the embryos had teratogenic effects in the respective higher dose groups. Survival in the Northwestern salamander, A. gracila, was 96, 89, 83, 67, 45 and 24% of controls at 4 days post-hatching following exposure at 0.002, 0.009, 0.20, 0.99, 2.58 and 21.4 mg 1,2-dichloroethane/ℓ, respectively. No teratogenic effects occurred in groups exposed at the four lowest dose levels, but 5 and 16% of embryos exposed at 2.58 and 21.4 mg/ℓ developed gross defects. Based on survival of the embryos at hatching and 4 days post-hatching, Black et al. (1982) reported LC_{50} values of ~34 mg/ℓ (both time periods) in trout, 4.52 and 4.40 mg/ℓ in frogs and 6.53 and 2.54 mg/ℓ in salamanders, respectively.

A 32-day bioassay of 1,2-dichloroethane was conducted in fathead minnows, P. promelas, exposed at 4, 7, 14, 29 and 59 mg/ℓ. During the tests, hatchability of embryos, frequency of abnormal embryos and survival of parental fish were not affected at any dose level (Benoit et al., 1982). The weight of the parental fish was significantly ($p=0.05$) reduced in the group exposed at 59 mg 1,2-dichloroethane/ℓ. These chronic tests were used to estimate a MATC between 29 and 59 mg 1,2-dichloroethane/ℓ.

Chronic toxicity tests of 28 days duration were conducted using the water flea, D. magna, exposed at 11-140 mg 1,2-dichloroethane/ℓ (Richter et al., 1983). The NOECs for reproduction and growth of adults were 11 and 42 mg/ℓ, respectively. The LOELs for reproduction and growth were 21 and 72 mg 1,2-dichloroethane/ℓ, respectively.

Kerster and Schaeffer (1983) conducted teratogenicity tests (abnormal elongation) of 1,2-dichloroethane in brine shrimp nauplii, A. salina. Nauplii were exposed at 0.25-25 mg/ℓ for 48 hours. Tests indicated that 1,2-dichloroethane was teratogenic and caused abnormal nauplii elongation.

6.3. PLANT EFFECTS

Toxicity tests in the freshwater green algae, Selenastrum capricornutum, were conducted for up to 96 hours at 1,2-dichloroethane concentrations as high as 433 mg/ℓ (U.S. EPA, 1978). Because this concentration did not cause a 50% decrease in algal growth for any duration, the EC_{50} value was reported to be >433 mg/ℓ. Some effects were noted, however, and the NOEC was <433 mg 1,2-dichloroethane/ℓ. In the green algae, Scenedesmus quadricauda, Bringmann and Kuehn (1980) reported a 7-day toxicity threshold for decreased cell multiplication (turbidity) of 710 mg 1,2-dichloroethane/ℓ. Knie et al. (1983) reported an EC_{50} value (duration not specified) of 130 mg/ℓ for 1,2-dichloroethane for the algae, Haematococcus plurialis.

In the marine algae, *Skeletonema costatum*, the U.S. EPA (1978) reported 24- to 96-hour EC_{50} values for decreased growth to be >433 mg 1,2-dichloroethane/ℓ. Some growth inhibition occurred at this level, since the NOEC was <433 mg/ℓ. Pearson and McConnell (1975) reported a 48-hour EC_{50} for decreased carbon assimilation of 340 mg 1,2-dichloroethane/ℓ in the marine algae, *Phaeodactylum tricornutum*.

6.4. RESIDUE

The U.S. EPA (1978) reported a BCF of 2 for fish tissue after fish were exposed to 0.096 mg 1,2-dichloroethane/ℓ for 14 days. The estimated half-life of 1,2-dichloroethane in fish tissue was 1-2 days.

Young et al. (1983) reported levels of 1,1- and 1,2-dichloroethane ranging from <0.3-16 and <0.3-54 μg/ℓ, respectively, in water and sludge samples from several California wastewater treatment facilities.

6.5. OTHER RELEVANT INFORMATION

Bringmann and Kuehn (1980) reported 48-hour toxicity threshold values of 135 and 1127 mg 1,2-dichloroethane/ℓ for decreased cell multiplication in bacteria (*Pseudomonas putida*) and protozoan (*Entosiphon sucatum*), respectively.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The Occupational Safety and Health Administration (Code of Federal Regulations, 1981) has established a TWA exposure level of 50 ppm (202 mg/m³) for 1,2-dichloroethane. The peak exposure level for a 5-minute excursion is 200 ppm (810 mg/m³) and the OSHA ceiling for any 3 hours of exposure is 100 ppm (405 mg/m³) (Code of Federal Regulations, 1981). NIOSH (1978b) recommended a TWA level of 1 ppm (4 mg/m³) with a 15-minute ceiling at 2 ppm (8 mg/m³). ACGIH (1984) adopted a TLV of 10 ppm 1,2-dichloroethane (40 mg/m³) and a STEL of 15 ppm (60 mg/m³) for 15-minute exposures. The TLV and STEL were recommended by ACGIH (1980) based on the hepatoxic effects (see Section 5.5.).

The inhalation limit for 1,1-dichloroethane established by OSHA (Code of Federal Regulations, 1981) was 100 ppm (405 mg/m³) for the TLV. ACGIH (1984) adopted a TLV of 200 ppm (810 mg/m³) and a STEL for 15-minute exposures of 250 ppm (1010 mg/m³). According to the documentation by ACGIH (1980), the adopted TLV and STEL were based on chronic toxicity data of Hofmann et al. (1971) and Dow Chemical Company (n.d.) (see Section 5.5.).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of 1,1- or 1,2-dichloroethane were not located in the available literature cited in the Appendix.

8. RISK ASSESSMENT

The carcinogenicity of 1,2-dichloroethane has been demonstrated in both rats and mice treated by gavage in the long-term NCI (1978a) bioassay. Male rats developed an increased incidence of squamous-cell carcinoma of the forestomach, hemangiosarcomas and subcutaneous fibromas (see Table 5-1). Female rats gavaged with 1,2-dichloroethane developed a significantly increased incidence of mammary gland adenocarcinoma. Mice of both sexes developed a high incidence of alveolar and bronchiolar adenoma, even though treatment was by the oral route. Male mice also developed an increased incidence of hepatocellular carcinoma. Mammary gland adenocarcinoma and uterine sarcoma and polyps also developed more frequently in treated female mice than in controls (see Table 5-1).

The only available long-term inhalation bioassay (Maltoni et al. 1980, 1982) did not demonstrate any carcinogenic effect in exposed rats or mice (see Table 5-2). Groups of Sprague-Dawley rats and Swiss mice of both sexes were exposed at four dose levels up to 250 to 150 ppm (1012 to 607 mg/m^3), 7 hours/day, 5 days/week for 78 weeks and observed for their lifetime. Hooper et al. (1980) evaluated the positive gavage carcinogenicity study (NCI, 1978a) and the inhalation study (Maltoni et al., 1980), and postulated possible reasons for the apparent opposite results of the two bioassays. Factors such as the purity of the test chemical, air contamination and dietary contamination were discussed, but not considered as among the most likely explanations of the discrepancy. Of major concern were the differences in strain of rats and mice used, effective dose levels and patterns of dosing or intercurrent premature mortality. The different susceptibilities of various strains of test animals have been established in other cancer and toxicity tests. Hooper et al. (1980) calculated effective dose levels for both studies and reported that each had two similar dose levels within the dosing range where significant tumor response occurred in the gavage study. The pattern of dosing by the different routes of exposure may have caused different effective whole-body levels of 1,2-dichloroethane. Inhalation of the daily dose occurred over a 7-hour period, allowing metabolism to occur and possibly result in lower blood levels of 1,2-dichloroethane and/or its effective metabolites. Gavage dosing, however, results in a bolus dose which may overwhelm the metabolic capacity and result in higher blood levels than if metabolism was not saturated. It was also suggested that gut microflora may produce carcinogenic metabolites of 1,2-dichloroethane prior to gastrointestinal absorption. Based on the premature mortality occurring in both studies at the high dose level, it was suggested that lifetime determination of carcinogenicity, especially for that developed late in the studies, may have been underestimated. Correction of tumor data based on life-table (actuarial) analysis may have altered the final carcinogenic response.

1,2-Dichloroethane was not teratogenic to offspring of rats or rabbits exposed via inhalation to 100 or 300 ppm (405 or 1214 mg/m^3), 7 hours/day during gestation (Schlacter et al., 1979), or mice exposed via drinking water at $\leq$50 mg/kg/day in a multigeneration study (Lane et al., 1982). The inhalation exposures were toxic to rabbit dams at $\geq$405 mg/m^3 and to rat dams and embryos at 1214 mg/m^3 (Schlacter et al., 1979). No effect on reproductive parameters of neonates or postnatal pups were observed in mice at drinking water concentrations of $\leq$50 mg/kg/day (Lane et al., 1982) or in rats at dietary concentrations up to 500 ppm (Alumot et al., 1976) or at inhalation concentrations up to 150 ppm (607 mg/m^3) (Rao et al., 1980).

Reports from the Russian literature, however, have associated occupational exposure of female glue workers with gynecologic and menstrual disturbances (Mukhametova and Vozovaya, 1972) and treatment of female rats at inhalation concentrations of 14 ppm (57 mg/m^3), 4 hours/day, 6 days/week prior to mating, and during gestation and lactation with decreased litter size, increased stillbirths, decreased birth weight, decreased postnatal survival and decreased post-weaning growth (Vozovaya, 1974). These findings are unreliable in view of the negative results obtained at higher concentrations by Rao et al. (1980).

Occupational exposure to 1,2-dichloroethane at $\leq$200 ppm (809 mg/m^3) has also been associated with gastrointestinal, liver, bile duct, thyroid, neurologic, lung and eye problems (U.S. EPA, 1984a).

Increased mortality was observed in rats treated chronically with 1,2-dichloroethane at a gavage dose of 95 mg/kg/day and mice at 299 mg/kg/day (NCI, 1978a). No effects were observed in rats at dietary levels $\leq$500 ppm for 2 years (Alumot et al., 1976). Munson et al. (1982) found no effects on the immune system of mice exposed to 1,2-dichloroethane in the drinking water at doses $\leq$189 mg/kg/day for 90 days; however, Borzelleca (1983) found unspecified kidney effects at unspecified dose levels in mice exposed via drinking water at $\leq$188 mg/kg/day for 90 days.

Long-term inhalation exposure of a variety of species to 1,2-dichloroethane at concentrations of 50-1000 ppm (202-4047 mg/m^3) for 7 hours/day, 5 days/week or 3000 ppm (12,142 mg/m^3) for 2 hours/day, 5 days/week has been associated with increased mortality and effects on the liver and kidney (Spreafico et al., 1980; Maltoni et al., 1980; Heppel et al., 1946; Spencer et al., 1951; Lioia et al., 1959a,b; Hofmann et al., 1971).

Based on the positive carcinogenesis by 1,2-dichloroethane in rats and mice (NCI, 1978a), IARC (1979) classified the compound as a positive animal carcinogen. The available positive mutagenicity data (see Tables 5-4, 5-5 and 5-6), especially when metabolic activation is provided, and the *in vitro* formation of a reactive metabolite were considered evidence supportive of the positive carcinogenicity bioassay. Because of the lack of cancer data in humans, IARC (1979) regarded 1,2-dichloroethane as a probable human carcinogen in light of the positive animal bioassay (Group 2B ranking).

The carcinogenic potency of 1,2-dichloroethane has been estimated based on the positive data from both rats and mice (NCI, 1978a), since no data regarding humans were available (U.S. EPA, 1984a). The incidence of hemangiosarcomas of the circulatory system of male rats was selected as the most sensitive tumor type that was not located at the site of direct contact with 1,2-dichloroethane. Using the linearized multistage model, the incidences of hemangiosarcoma (0/40, 9/48, 7/27) among control, low dose and high dose males that survived $\leq$50 weeks and the human equivalent doses (0, 4.85 and 9.80 mg/kg/day) were used to calculate the q_1^*. Using correction factors for species-to-species extrapolation and time-to-death, resulted in a $q_1^*=6.9\times10^{-2}$ $(mg/kg/day)^{-1}$. The upper-bound estimate of the cancer risk from ingesting water contaminated at 1 µg/ℓ was 2×10^{-6}. By inhalation, the carcinogenic potency was estimated to be $q_1^*=6.6\times10^{-6}$ $(\mu g/m^3)^{-1}$, assuming 33% absorption and a human daily air intake of 20 m^3 (U.S. EPA, 1984a).

The NCI (1978b) bioassay exposed rats and mice by inhalation to 1,1-dichloroethane (see Table 5-3) for 78 weeks. There is evidence that 1,1-dichloroethane is a probable human carcinogen. This conclusion is based on the following: 1) multiple tumor types in both an oral rat bioassay and an oral mouse bioassay; 2) suggestive evidence in two other bioassays, one which showed an elevated increase in lung tumors with intraperitoneal injection and a second study which showed a significantly increased incidence of benign lung tumors with skin application of 1,1-dichloroethane; 3) demonstrated evidence of reactive metabolites of 1,1-dichloroethane and formation of DNA adduct; and 4) evidence that 1,1-dichloroethane is also a mutagen.

There is direct animal evidence for carcinogenicity by the oral (gavage) route of exposure, but the only specific bioassay data for inhalation exposure are a negative rat and mouse study. Because of the presence of distant site tumors in the oral studies, it is likely that 1,1-dichloroethane is also carcinogenic by inhalation exposure. The negative findings in the rat and mouse inhalation studies do not contradict the indirect, suggestive and ancillary evidence for the likelihood of 1,1-dichloroethane being carcinogenic by inhalation.

The U.S. EPA is using, on an interim basis, a proposed classification scheme for evaluating the weight-of-evidence for carcinogenicity (U.S. EPA, 1984). Using this classification, the positive findings in the oral rat and mouse studies would be considered as a sufficient level of evidence in experimental animals. THe sufficient level of animal evidence, together with an absence of epidemiologic data, provides a basis for an overall weight-of-evidence ranking of Group B2, meaning that 1,1-dichloroethane is "probably" carcinogenic in humans.

Applying the IARC classification scheme, which EPA has used in the past, the positive findings in the experimental animals and the absence of epidemiologic data provide an overall weight-of-evidence ranking of Group 2B, meaning that 1,1-dichloroethane is "probably" carcinogenic in humans.

While the "probable" carcinogenicity conclusion obviously applies to ingestion exposure since the positive evidence comes from gavage experiments, it is likely that 1,1-dichloroethane is a probable carcinogen for humans by inhalation exposure. In view of the evidence, it is prudent to consider 1,1-dichloroethane to be carcinogenic by inhalation exposure although the potency may vary from that estimated from gavage. Research investigations to verify this assessment conclusion should be implemented.

Assuming that 1,1-dichloroethane is carcinogenic for humans, upper-bound incremental unit cancer risks have been estimated for both ingestion and inhalation exposure. The development of these unit risk estimates is for the purpose of evaluating the "what if" question: If 1,1-dichloroethane is carcinogenic for humans, what is the possible magnitude of the public health impact? The upper-bound estimate of 1,1-dichloroethane's carcinogenic potency is $q_1^* = 9.1 \times 10^{-2}$ mg/kg/day based upon the occurrence of hemangiosarcomas in the NCI gavage rat study. The upper-bound estimate of the incremental cancer risk due to 1 µg/ℓ of 1,1-dichloroethane in drinking water is 2.6×10^{-6}, based upon the previously mentioned potency value. Two upper-bound estimates of the incremental cancer risk due to 1 µg/m³ of 1,1-dichloroethane in air are calculated: 2.6×10^{-5} on the basis of hemangiosarcomas in the NCI gavage study, and 1.0×10^{-6} on the basis of a negative inhalation study by Maltoni et al. (1980). The inhalation unit risks are presented as two values in recognition of the uncertainties associated with the differing data that were used to estimate the values. The upper-bound nature of these estimates is such that the true risk is not likely to be exceeded and may be lower.

1,1-Dichloroethane was positive for reverse mutation with and without metabolic activation in unspecified strains of S. typhimurium (Riccio et al., 1983) and for enhanced viral transformation in Syrian hamster embryo cells (Hatch et al., 1983).

No teratogenic effects were observed in the offspring of rats exposed by inhalation to 1,1-dichloroethane at 3800 and 6000 ppm (15,380 and 24,285 mg/m^3), 7 hours/day during gestation; however, fetotoxicity, as evidenced by an increased incidence of delayed ossification of sternebrae, was observed at the high exposure level (Schwetz et al., 1974). Both levels were toxic to dams resulting in decreased food consumption and body weight, and increased liver weight. Gostinskii (1966) reported that inhalation exposure of rats to 7800 mg/m^3 for 6 hours on day 10 of gestation resulted in death of dams, while 6500 mg/m^3 was lethal to fetuses.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

The chronic toxic effects of 1,2-dichloroethane, useful for the derivation of an RQ, have been reviewed in Section 5.5. and by the U.S. EPA (1983a). A summary of the available data showing toxic effects following subchronic and chronic exposure, human MED levels, CSs and RQ values is presented in Table 9-1.

The occupational morbidity study by Kozik (1957) was the only toxicity study in humans that contained sufficient information to determine a CS and an RQ. The incidence of liver and gall bladder disease was increased, occurring in 19/83 workers. The average exposure level for most workers was 10-15 ppm (40.5-60.7 mg/m³) (NIOSH, 1976). Using 10 ppm (40.5 mg/m³) as the exposure level for the workday (10 m³/8 hours) and assuming 100% absorption efficiency, the human MED for continuous exposure would be 289 mg/day for a 70 kg adult (40.5 mg/m³ x 5 days/7 days x 10 m³/day). The RV_d for the human MED would be 1.8, and the RV_e for liver and gall bladder disease would be 8. The CS and RQ would, therefore, be 14.4 and 1000, respectively (see Table 9-1). In animals, toxic effects following chronic and subchronic exposure, primarily by inhalation, include histological and functional changes in the liver and kidneys and increased mortality. To calculate the MED for the oral study in rats (NCI, 1978a), the dose of 95 mg/kg/day, which was administered 5 days/week for 546 days followed by a 161-day observation period, was expanded over a 7-day week and over the entire 707-day duration of the study as follows: 95 mg/kg/day x 5 days/7 days x 546 days/707 days = 52.4 mg/kg/day. The resultant TWA dose of 52.4 mg/kg/day was multiplied by the cube root of the ratio of rat weight (0.5 kg in the study) to the weight of a 70 kg man to convert for interspecies extrapolation and by 70 kg to express the MED in mg/day.

TABLE 9-1

Composite Scores for Chronic Toxicity of 1,2-Dichloroethane

Species	Exposure: Level and Route	Exposure: Duration	Chronic Human MED (mg/day)	RV_d	Effects	RV_e	CS	RQ	Reference
Human	10 ppm (40.5 mg/m³) inhalation	occupational	289	1.8	Liver and gall bladder diseases	8	14.4	1000	Kozik, 1957
Rat	95 mg/kg/day oral	5 days/week for 546 days followed by 161 days observation	706	1.2	Increased mortality	10	12	1000	NCI, 1978a
Guinea pig	200 ppm (809 mg/m³) inhalation	7 hours/day; 5 days/week x 8 months	1126	1	Slight parenchymatous degeneration of the liver	6	6	1000	Spencer et al., 1951
Guinea pig	400 ppm (1619 mg/m³) inhalation	7 hours/day; 5 days/week x 8 months	2253	1	Increased mortality	10	10	1000	Spencer et al., 1951
Dog	400 ppm (1619 mg/m³) inhalation	7 hours/day; 5 days/week x 8 months	1479	1	Slight fatty changes in liver and kidney	5	5	5000	Heppel et al., 1946
Rat	200 ppm (809 mg/m³) inhalation	7 hours/day; 5 days/week x 7 months	1285	1	Increased mortality	10	10	1000	Heppel et al., 1946
Rabbit	3000 ppm (12,142 mg/m³) inhalation	2 hours/day; 5 days/week x 90 days	590	1.3	Anemia, leukopenia, thrombocytopenia, hyperplasia of granuloblastic and erythroblastic parenchyma of bone marrow; altered liver and kidney function with necrosis	8	10.4	1000	Lioia et al., 1959a,b; Lioia and Elmino, 1959; Lioia and Fondacaro, 1959
Rat	50 ppm (202 mg/m³) inhalation	7 hours/day; 5 days/week x 12 months	321	1.7	Increased SGPT levels, increased γ-GT levels, decreased SGOT levels, decreased serum cholesterol	2	3.4	5000	Spreafico et al., 1980
Mouse	150 ppm (607 mg/m³) inhalation	7 hours/day; 5 days/week x 78 week	866	1.1	Increased mortality	10	11	1000	Maltoni et al., 1980

To calculate MEDs from the inhalation studies, the concentrations in mg/m³ were expanded over 24-hour days and 7-day weeks, multiplied by the daily inhalation volumes of the respective species, divided by the body weight of the respective species, multiplied by the cube root of the ratio of the animal body weight to the weight of a 70 kg man and multiplied by 70 kg. Absorption was assumed to be 100%. The animal body weights used in these calculations were 0.35 kg for rats, 0.43 kg for guinea pigs, 14 kg for dogs, 3.7 kg for rabbits and 0.03 kg for mice. The inhalation volumes were 0.223 m³/day for rats, 0.224 m³/day for guinea pigs (Guyton, 1947), 1.5 m³/day for dogs (Hertzberg and Dourson, 1983), 1.15 m³/day for rabbits (Guyton, 1947) and 0.039 m³/day for mice. Although the human MED values derived from the effective animal exposure levels varied ~5-fold, all MEDs were relatively high and resulted in RV_d values of <2. The effects varied from minor enzyme level changes (Spreafico et al., 1980) to increased mortality so that RV_e values ranged from 1-10. CSs based on the toxic effects in animals in the long-term studies ranged from 3.4-12, all being less than or near the CS of 14.4 from the human toxicity data (Kozik, 1957). Based on the available chronic toxicity data, the CS of 14.4 and corresponding RQ of 1000 determined from liver and biliary disease in occupationally exposed humans (Kozik, 1957) are selected as the most appropriate ranking values of the chronic toxicity of 1,2-dichloroethane (Table 9-2).

In a previous determination of the RQ for 1,2-dichloroethane (U.S. EPA, 1983a), the study of Kozik (1957) was also chosen as the most appropriate basis for the RQ. Although the RQ value of 1000 was determined in U.S. EPA (1983a) and the present determination, the CSs are different. The difference is due to the fact that in the U.S. EPA (1983a) calculation of the MED absorption was assumed to be 50%, while in the current methodology, 100% absorption is assumed.

TABLE 9-2

1,2-Dichloroethane

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose*:	289 mg/day
Effect:	liver and gall bladder diseases
Reference:	Kozik, 1957
RV_d:	1.8
RV_e:	8
Composite Score:	14.4
RQ:	1000

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*Equivalent human dose

The MEDs, RV_ds and CSs for the animal inhalation studies also differ in the two determinations. In the U.S. EPA (1983a) determination, inhalation exposures were assumed to be equivalent among species; therefore, exposures were converted directly to human MEDs by multiplying by the human daily breathing volume of 20 m^3/day. Absorption was assumed to be 50%. In the current methodology, absorption is assumed to be 100% and animal inhalation volumes and animal body weights are used. The resultant animal dose is converted to an equivalent human dose using the cube root of the body weight ratio approximation.

The MEDs, RV_ds and CSs for the oral study in rats (NCI, 1978a) differ in the two determinations because in the previous determination, the dose was not expanded over 7 days or over the 707-day duration of the study.

Another difference between the two determinations is that U.S. EPA (1983a) included data from a 6-week study for comparison. Including these data in the current determination was deemed unnecessary because of the abundance of data from longer-term studies.

Data regarding on the chronic toxicity of 1,1-dichloroethane, which are useful for the derivation of a CS and an RQ, were reported only in the multiple species inhalation study conducted by Hofmann et al. (1971). The gavage study by NCI (1978b) and the inhalation study by the Dow Chemical Company (n.d.) reported that no toxic effects were evident even at the highest dose level tested; therefore, these studies are not useful in determining an effect-level and calculating a CS and an RQ. Hofmann et al. (1971) reported that no effects were seen in rats, guinea pigs or rabbits exposed at 500 ppm (2024 mg/m^3), 6 hours/day, 5 days/week for 13 weeks and additionally at 1000 ppm (4047 mg/m^3) for 13 weeks. In cats, however, exposure on this regimen resulted in increased blood urea nitrogen and histological evidence of renal injury. An exposure level of 750 ppm (3036 mg/m^3) as the TWA for the 26-week study (13 weeks at 500 ppm, 13 weeks at 1000 ppm) can be used as the LOAEL. The human MED of 5234 mg/day was calculated assuming a daily inhalation volume of 1.26 m^3 for cats and an absorption efficiency of 100%. The experimental exposure intervals were expanded to represent continuous exposure, multiplied by 1.26 m^3/day, divided by the cat body weight of 3.3 kg and multiplied by the cube root of the ratio of the cat body weight to the human body weight of 70 kg and by 70 kg to express the MED as mg/day: MED = 3036 mg/m^3 x 6 hours/24 hours x 5 days/7 days x 1.26 m^3/day ÷ 3.3 kg x $(3.3\ kg/70\ kg)^{1/3}$ x 70 kg. Based on the human MED of 5234 mg/day, the RV_d would be 1. The appropriate RV_e for the severity of renal damage with impaired function is 7. The product of the RV_d and RV_e, the CS, is 7, which corresponds to an RQ of 1000 (Tables 9-3 and 9-4).

The RQ is the same as that derived in a previous determination (U.S. EPA, 1983b). The same study was used as the basis for the RQ; however, the CSs differ. As explained above for 1,2-dichloroethane, the difference is due to differences in the former and the current methodologies. Furthermore, in the previous determination by U.S. EPA (1983b), the MED was divided by an uncertainty factor of 10 to approximate chronic exposure. In the current determination, the use of the uncertainty factor was deemed unnecessary. As discussed in Chapter 8, pharmacokinetic data indicate that steady state would be reached in 6 months of exposure, and 1,1-dichloroethane does not appear to elicit irreversible toxic effects that would become more severe with longer exposure.

TABLE 9-3

Composite Scores for Chronic Toxicity of 1,1-Dichloroethane in Cats

Exposure		Chronic Human MED (mg/day)	RV_d	Effects	RV_e	CS	RQ	Reference
Level and Route	Duration							
750 ppm (3036 mg/m^3)	26 weeks	5234	1.0	Histologic evidence of renal damage and increased blood urea nitrogen	7	7	1000	Hofmann et al., 1971

TABLE 9-4

1,1-Dichloroethane

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose*:	5234 mg/day
Effect:	renal injury with histological damage and increased blood urea nitrogen
Reference:	Hofmann et al., 1971
RV_d:	1
RV_e:	7
Composite Score:	7
RQ:	1000

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*Equivalent human dose

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

The NCI (1978a) bioassay of 1,2-dichloroethane demonstrated a carcinogenic effect in male rats (forestomach squamous-cell carcinomas, hemangiosarcomas, subcutaneous fibromas), female rats (mammary adenocarcinomas), male mice (alveolar and bronchiolar adenomas, hepatocellular carcinomas) and female mice (alveolar and bronchiolar adenomas, mammary adenocarcinomas, endometrial stromal sarcomas and polyps) following gavage dosing (see Table 5-1). Chronic inhalation of 1,2-dichloroethane did not produce an increased incidence of any tumor type in rats or mice (see Section 5.1. and Table 5-2) (Maltoni et al., 1980). Hooper et al. (1980) suggested that the apparent discrepancy regarding the carcinogenicity of 1,2-dichloroethane may result from differences in susceptibility of the different animal strains, intercurrent premature mortality, or effective dose levels and patterns of dosing by the different routes (see Chapter 8). Based on the positive evidence of carcinogenesis in rats and mice (NCI, 1978a), U.S. EPA concluded that there was sufficient evidence to classify 1,2-dichloroethane as a Group B2 chemical. This classification reflects the positive animal carcinogenicity, but insufficient human data.

The F-factor for carcinogenicity of 1,2-dichloroethane was calculated by the U.S. EPA (1983b) based on the incidence of alveolar and bronchiolar adenoma in male mice (NCI, 1978a). Data reported by Van Duuren et al. (1979) support the conclusion that the lung is a site of action, since a high level of benign lung papillomas occurred in mice exposed dermally to 1,2-dichloroethane. The incidence of this tumor type was selected as the most appropriate for potency derivation because it showed the greatest increase compared with controls and tumors at this site were remote from the gastrointestinal tract. Data for the derivation of the F-factor are summarized in Table 9-5. The unadjusted $1/ED_{10}$ was calculated using the linearized multistage model developed by Kenneth Crump and adopted by the U.S. EPA (Federal Register, 1980). The F factor was obtained by multiplying by the cube root of ratio of the weight of a man (70 kg) to the weight of the mouse (0.035 kg) to correct for interspecies extrapolation and by the cube of the ratio of the lifespan of the animal to the duration of the study.

Since the U.S. EPA (1984a) calculated a q_1* for 1,2-dichloroethane (see Chapter 8) based on the incidence of hemangiosarcomas among male rats surviving $\geq$50 weeks in the NCI (1978a) study, an F-factor for carcinogenicity can also be determined using these data. The incidence of hemangiosarcomas among control, low dose and high dose males that survived $\geq$50 weeks was 0/20, 9/48 and 7/27, respectively. Table 9-6 summarizes the incidence data and transformed doses used in the F-factor calculation. The $1/ED_{10}$ and F factor were calculated as described above, but using the rat body weight (0.5 kg). No correction for lifespan was necessary because the duration of the experiment was equal to the lifespan. The potency factor for these data on hemangiosarcomas was 0.36, which is slightly higher than the value of 0.27 determined for pulmonary adenomas in mice (see Table 9-5). The F-factor of 0.36 is, therefore, selected as the most appropriate value for the carcinogenicity of 1,2-dichloroethane. According to the hazard ranking scheme for carcinogenic potency (U.S. EPA, 1984b), 1,2-dichloroethane would be in Potency Group 4 and have a low hazard ranking (based on IARC Group 2B and F-factor <1).

Data regarding the carcinogenicity of 1,1-dichloroethane are limited to that reported by the NCI (1978b) (see Table 5-3). This bioassay provided limited evidence of carcinogenicity, since high mortality among control and treated rats and mice precluded the possible detection of late-developing

TABLE 9-5

Derivation of Potency Factor (F)
Agent: 1,2-Dichloroethane

Reference:	NCI, 1978a		
Exposure route:	gavage		
Species:	mice		
Strain:	B6C3F1		
Sex:	male		
Vehicle or physical state:	corn oil		
Body weight[a]:	0.035 kg[a]		
Duration of treatment:	546 days		
Duration of study:	637 days (high dose)	630 days (low dose)	630 days (control)
Lifespan of animal:	730 days[b]		
Target organ:	lung		
Tumor type:	alveolar/bronchiolar adenoma		
Experimental doses/ exposure:	195 mg/kg/day	97 mg/kg/day	0 mg/kg/day
Transformed doses (mg/kg/day):	119	60	0
Tumor incidence:	15/48	1/47	0/19
Unadjusted $1/ED_{10}$:	0.014		
$1/ED_{10}$ (F factor):	0.27		

[a] Reported

[b] Assumed

TABLE 9-6

Derivation of Potency Factor (F)
Agent: 1,2-Dichloroethane

Reference:	NCI, 1978a		
Exposure route:	gavage		
Species:	rat		
Strain:	Osborne-Mendel		
Sex:	male		
Vehicle or physical state:	corn oil		
Body weight[a]:	0.50 kg[a]		
Duration of treatment:	546 days		
Duration of study:	707 days (high dose)	770 days (low dose)	700 days (control)
Lifespan of animal:	770 days[a]		
Target organ:	circulatory system		
Tumor type:	hemangiosarcoma		
Experimental doses/ mg/kg/day exposure:	95 mg/kg/day	47 mg/kg/day	0.0
Transformed doses (mg/kg/day):	52.4	23.8	0.0
Tumor incidence[b]:	7/27	9/48	0/20
Unadjusted $1/ED_{10}$:	0.07		
$1/ED_{10}$ (F factor):	0.36		

[a] From experimental data

[b] Reported tumor incidence for male rats surviving ≥50 weeks

tumors. Positive correlations between dosage and the incidence of mammary gland adenocarcinomas and hemangiosarcomas in female rats were regarded as suggestive evidence of the carcinogenicity of 1,1-dichloroethane (NCI, 1978b). Hepatocellular carcinoma and lung adenoma in treated male mice were increased, but not significantly compared with controls.

Based on the limited evidence of carcinogenicity in animals, the similarity in response with 1,2-dichloroethane and the lack of evidence in humans, 1,1-dichloroethane is classified on an interim basis as a Group C chemical according to the U.S. EPA classification scheme. Based on the interim nature of this classification, it is not appropriate to calculate an F-factor for 1,1-dichloroethane. At a later date, after a review of detailed data from NTP, such a derivation may be appropriate.

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in December 1984 with the exception of the TOXLINE, which was searched in July 1984 and kindly supplied by Dynamac Corporation. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

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Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

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Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technology Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

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Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. USDI, Fish and Wildlife Serv. Res. Publ. 137. Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California. State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. PB-269605. Prepared for the U.S. EPA, Washington, DC.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. U.S. EPA, Office Pesticide Programs. Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.

In addition, the following 8E Status Reports were reviewed:

Status Report 8EHQ-0680-0345

Status Report 8EHQ-0979-0310